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## Combination Cytotoxic Chemotherapy in Advanced Disseminated Breast Carcinoma

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The therapeutic value of cytotoxic chemotherapy for advanced breast carcinoma has not been clearly delineated although recent clinical studies demonstrate a substantial degree of tumor-inhibitory action by a variety of individual chemical agents. Short-term regressions with clinical remission of several months duration may be induced in 30-75% of patients treated with such alkylating agents as thio-TEPA, Cytosan and Chlorambucil, or the anti-metabolites, Methotrexate or 5-Fluorouracil (1-6). Despite this high incidence of response, controversy persists regarding the proper time to employ these potentially toxic drugs in the natural course of metastatic breast carcinoma. Considerable doubt also remains among clinicians as to the single drug of choice, if any, the optimal method of drug administration and the relationship of chemotherapy vis-a-vis the various forms of endocrine or ablative therapy. No reliable data are yet available to indicate whether any of the diverse and often distinctive patterns of metastatic organ involvement encountered commonly by the practicing clinician may respond preferentially to one or another of the oncostatic agents. Although the synergistic effect of drug combinations on animal tumors have been well known for many years (7, 8), the clinical literature has been devoid, until now, of any substantial study of combined simultaneous and sustained administration of two or more different cytotoxic agents in breast carcinoma.

We have attempted to assess some of these varied aspects of the chemotherapy of breast carcinoma, particularly the question whether clinical synergism can be safely obtained by the use of simultaneous drug combinations. Over a five-year period, 113 cases of advanced breast carcinoma were treated with simultaneous intermittent courses of Methotrexate (MTX) plus priming and maintenance doses of thio-TEPA (TP). The term "combination cytotoxic chemotherapy" was applied to this use of near-toxic, effective dose levels of two or more cytotoxic agents capable of inhibiting tumor growth by different biochemical mechanisms. Preliminary results of this therapy with a simultaneous alkylating agent (thio-TEPA) and an antimetabolite (Methotrexate) were published (9) in 1963. Since this report, three cytotoxic agents (5-Fluorouracil,

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MTX, TP) have been employed simultaneously in certain "desperate" situations, specifically in all patients presenting with massive metastatic hepatomegaly (10), and in some with lymphangitic pulmonary carcinomatosis or rapidly-growing cerebral metastases. The combined toxicity of these drug combinations was tolerable, under proper safeguards, even though each agent was given to its point of clinical toxicity.

The *sine qua non* for the safe use of cytotoxic drug combinations include wide clinical experience and knowledge of the toxicity, pharmacology, dosimetry and mechanism of action of each agent alone. Most important has been the necessary modification of dosage in accordance with the clinical condition of each patient. Prior to deciding on dosage, patients were always assigned to "good" or "poor risk" categories dependent on general medical status, pattern and extent of metastases and lapsed time from previous therapy. Early in our study it was emphasized (9) that antimetabolite dosage could not be prescribed on the basis of body weight or without careful daily scrutiny of the patient during the initial course of combination chemotherapy. Important supportive measures appear to have been instrumental in maintaining a relatively good tolerance to combination cytotoxic chemotherapy. These included the use of aqueous crystalline testosterone as an anabolic and hematostimulative agent (as well as for any antineoplastic action) and parenteral B12 to partially protect the bone marrow against antimetabolite depression. Oral steroids in modest doses were given to those cases with "desperate" metastatic organ involvement. Some aspects of this five-year experience with combination cytotoxic chemotherapy have been presented elsewhere (9-11).

#### CLINICAL MATERIAL

All patients with advanced breast carcinoma were accepted for combination chemotherapy unless there had been a prior history of major gastrointestinal bleeding. In the first 40 patients treated from 1959-1961 (Group I), simultaneous courses of oral Methotrexate (MTX) and intramuscular priming and maintenance thio-TEPA (TP) were employed as illustrated in Chart I. Androgen therapy was continued in 37 of these 40 Group I patients despite the fact that they were suffering from testosterone recurrent or resistant disease. Aqueous crystalline testosterone was continued at doses of 50-150 mg per week to a masculinizing level for hemato-stimulation. Three patients received no testosterone during the first three months on combined chemotherapy. In Group I, 37 of the 40 patients had multifocal late metastatic disease recurrent after radiotherapy, oophorectomy and testosterone; three had also failed to respond to estrogens; one was post-adrenalectomy. Two of the only three patients without previous hormonal or ablative therapy were "fresh" cases of advanced inflammatory carcinoma.

Since the combination of TP + MTX was found to be relatively safe, an additional group of 73 patients (Group II) were treated (1962-1965) without necessarily waiting to determine whether metastases would have been hormo-

nally responsive to testosterone. Forty-three in this group had had no previous endocrine or ablative measures; eighteen had had previous surgical castration; five, x-ray castration; three were post-adrenalectomy. Testosterone was initiated with the TP + MTX in sixty-three and continued in ten, always to masculinization. The priming dose of testosterone was initiated at a dose of 300–400 mg per week for three weeks to masculinization then maintained with masculinization throughout the course of chemotherapy at a dose of 50–150 mg per week. B-12 was given once per week (200 meg I.M.) to moderate the depressive effect of antimetabolite therapy (MTX and/or FU) on erythrocyte production. When metastatic disease had become demonstrably recurrent on

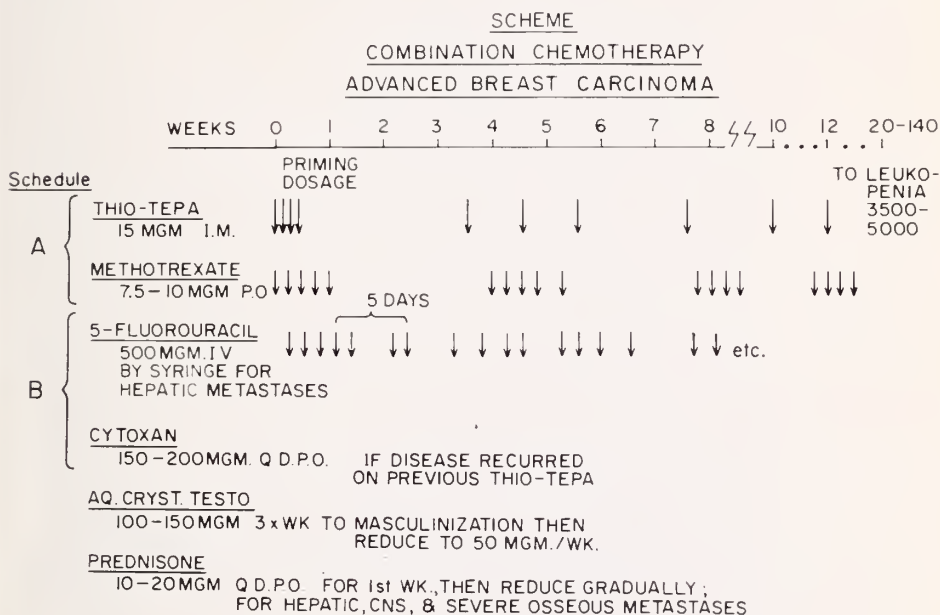


Chart I

Schematic representation of dosage schedules employed during combination chemotherapy; Schedule B was employed when metastatic disease was either resistant to or recurrent on Schedule A.

or was resistant to the combination of TP + MTX, a trial of Cytosin (CYT) and/or 5-Fluorouracil (FU) was undertaken. Although the initial combination of TP + MTX was always started simultaneously, the CYT and FU were often begun a few days apart. Nine patients presenting with metastatic hepatomegaly were treated with an initial triple drug combination consisting of 5-Fluorouracil (FU) plus MTX either TP or Cytosin (CYT), accompanied by steroids and androgens. Thus, the 73 Group II cases comprised a series consisting of initial simultaneous double or triple cytotoxic agents, accompanied by androgens and steroids followed 1–26 months later by sequential or simultaneous FU and Cytosin. All advanced metastatic disease presenting for chemotherapy were treated with this combination multiple cytotoxic approach since 1962 (Chart I).

The distribution and proportion of cases presenting with CNS metastases, major hepatic metastases, or diffuse osseous metastases was approximately the same in both Group I and Group II. Median age in both groups was 52 years.

#### DRUG DOSAGE

Thio-TEPA was given in an initial 60 mg priming dose over a 4-day period (Chart I), 15 mg intramuscularly daily. This was followed three weeks later by 15 mg maintenance doses of thio-TEPA at whatever intervals were necessary to maintain a minimal but definite leukopenia. Usually in the first three months of thio-TEPA maintenance therapy, 15 mg every seven to ten days was needed to maintain a mild persistent leukopenia; later 15 mg every 14 to 21 days was sufficient to maintain the leukopenia. Methotrexate was given in intermittent oral courses, each until the first sign of antifol stomatitis appeared. The second course of Methotrexate was usually given three to four weeks after the first. Dosage varied from 5–10 mg, q.d. for from 4–9 days. Dosage varied considerably from patient to patient as detailed previously (9). Combination chemotherapy with at least two courses of Methotrexate plus thio-TEPA were completed in 36 of 40 Group I patients, and in 62 of 73 Group II patients.

Cytosin was administered preferably by mouth at doses of 150–200 mg daily for twenty days per month. If the oral route induced nausea or vomiting uncontrollable by Tigan or Compazine the Cytosin was administered intravenously at doses of 300–500 mg daily to a total priming dose of 2–3 Gm. The appearance of alopecia and leukopenia indicated an adequate dosage. Under favorable circumstances Cytosin was administered for many months orally in 20-day cycles each month as long as platelets and hemoglobin were reasonably well-maintained. Leukopenia was not a contraindication to Cytosin unless at levels less than 2000 WBC per cu mm. High fluid intake was encouraged to avoid Cytosin-induced hemorrhagic cystitis. Whenever Cytosin and Fluorouracil were given intravenously on the same day a single needle was employed with separate syringes.

The initial priming dosage ("antipyrimidine titration") of 5-Fluorouracil was administered by simple syringe technique intravenously in 500 mg doses daily for four or five days. The crucial fifth dose was withheld in the poorest risk patients. After an invariable three-day pause a maintenance schedule of three doses per week during the second and third weeks was usually given. Stomatitis, diarrhea or leukopenia were deemed signs of adequate dosage in the second or third weeks of FU therapy and necessitated reduction or temporary omission of doses. Later maintenance doses of 500–700 mg of FU every 4–7 days to the limit of mild leukopenia were given until metastases had failed to respond or recurred. When Cytosin and 5-FU were given concomitantly there was relatively little reduction in dosage unless definite hematodepression preceded the start of the CYT-FU combination. When MTX was administered with FU, the appearance of any stomatitis signalled prompt stoppage of MTX, but 5-FU was usually resumed on a maintenance regimen four to five days after G.I. toxicity subsided.



The use of these drug combinations is synoptically shown in Chart I. The dosage and timing of Combination A was employed initially in all 40 Group I cases and 64 of the Group II cases. Combination B was not used initially in any case in this study, but was reserved for failure on Combination A. Triple combinations with 5-FU were employed in nine hepatic metastases cases in Group II.

TABLE I  
*Combination Chemotherapy Toxicity and Complications*

	Group I	Group II (TP + MTX CYT a/oFU)
	1951-1961	1962-1965
Stomatitis.....	40	65
Leukopenia.....	38	64
Anorexia.....	34	60
Nausea.....	31	52
Epigastric pain.....	21	25
Vomiting.....	12	21
Fever.....	8	19
Thrombopenia.....	11	6
Alopecia.....	7	51
Diarrhea.....	6	17
Rash.....	5	8
G.I. bleeding.....	3	3
Purpura.....	3	5
Nasal bleeding.....	3	4
Induced hypoplastic marrow.....	2	2
Acute fatal shock with pancytopenia (post- adrenalectomy).....	1	1
Cystitis.....	1	14 (Cytosan)
Erysipelas.....	3	11
Herpes Zoster.....	2	13
Acute Pyogenic Skin Infection.....	5	10
Total Patients.....	40	73 (52 with CYT, 19 with FU)
Drug Deaths.....	2	2

#### TOXICITY

The toxic manifestations in 113 patients initially given thio-TEPA and Methotrexate are summarized in Table I. Only six cases developed life-impairing toxicity, resulting in four drug-induced fatalities. In the first instance, an adrenalectomized patient in terminal condition with innumerable superficial and deep organ metastases went into fatal shock four days after TP + MTX had been started. Sudden pancytopenia accompanied this abrupt demise which might have been deferred with a smaller dose of antifol buttressed by larger doses of steroids. Three patients died 12-13 days after the onset of TP + MTX.

In one, an adrenalectomy and oophorectomy were performed (against medical opinion) at the height of the antifol-thioTEPA action in a patient with massive vena caval obstruction and extensive chest wall involvement. She died six days post-operatively with severe agranulocytosis and generalized bleeding. In another patient, a fatal pancytopenia was induced due to diffuse bone metastases, recent widespread radiation and prolonged protein depletion associated with mental depression and cachexia. In this case the dose of TP and MTX was deemed in retrospect to have been too high in view of the several severe "poor risk" factors. A fourth patient with poor renal function secondary

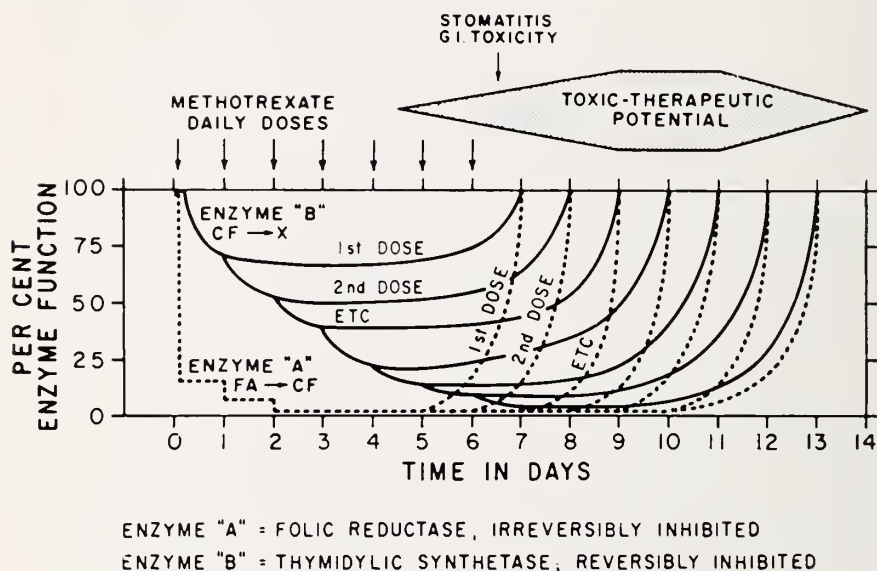


Chart II

The time-dose relationship of Methotrexate therapeutic effect vs. its rapid anti-enzyme action is shown schematically when antifol is given to patients in daily oral doses. The inhibitory antifol action is exerted on two sets of related enzymes, generically designated as "folic reductases" and "thymidyllic synthetases". The maximum therapeutic and toxic effects become manifest three to four days after stopping the drug. Recovery in these enzymes usually occurs about one week after the patient has received any dose or series of doses of antifol.

to hypercalcemia from diffuse bony metastases, died with severe unexpected pancytopenia, due probably to delayed renal excretion of MTX.

The relative safety of the TP and MTX appeared to be the result of scaling down of MTX dosage in accordance with the clinical features in each individual case. No arbitrary predetermined protocol of MTX dosage was employed. By adhering to the concept of a weekly aggregate dosage given in daily oral doses (Chart II) it was possible to gradually approach the toxic-therapeutic antifol "titration" level without inducing fatal toxicity except in unusual instances. Chart III illustrates the wide range of aggregate dosage required to induce the antifol effect. Poor risk patients became toxic after 3 days on as little as 5-7.5 mg per day. The variable MTX dosage necessary to induce the antifol state



reflected differing endogenous folic acid reserves. Clinical factors reducing the folic acid reserves are shown in Table III. Three or more courses of Methotrexate were given to 46 good risk patients, or 40% of the total of 113 treated.

Cytosan cystitis occurred in 14 patients of a total of 52 receiving the drug. This necessitated the withdrawal of drug in each patient so affected. The toxicity of sequential or combined FU and CYT was difficult to separate from the effects of preterminal metastatic dissemination in many Group II patients. Myelophthisic and hypoplastic marrows occurred terminally in 19 cases, in part at least due to the cumulative effects of combined sequential chemotherapy.

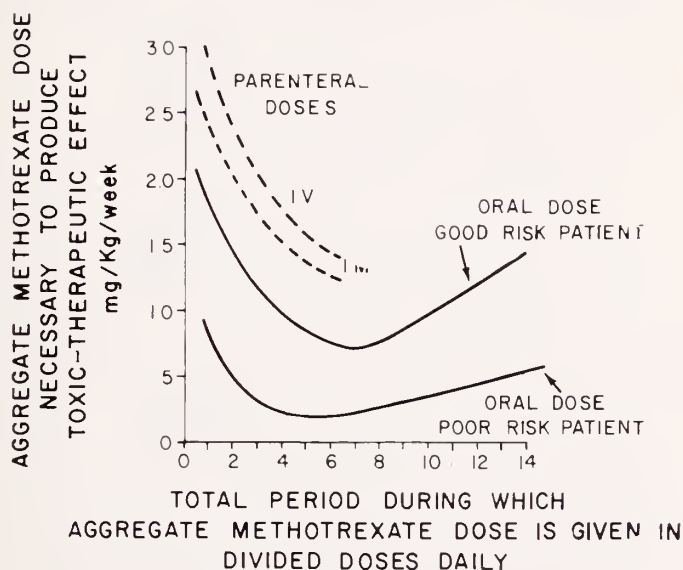


Chart III

The wide variation in tolerance to Methotrexate is schematically illustrated by this dosage template. Poor risk patients became toxic on 15-20 mg per week compared to good risk patients who required 50-80 mg. The antifol "titration" could be most gradually and safely approached by dosage given over a 5-7 day period.

Erysipelas, herpes zoster and staphylococcal skin infections occurred in more than one-fifth of the patients receiving combination chemotherapy (Table 1).

## RESULTS

### *Regression Response Rates*

Regression and remission of advanced breast carcinoma (Table II) were observed after TP and MTX combination therapy in 25 or 60% of a total of the 40 Group I cases treated from 1959-1961 and in 59 of 73 or 81% of those Group II cases initially treated from 1962-1965 with TP and MTX. These results in Group II include seven inflammatory carcinomas and nine hepatic metastases cases (Fig. 1) given triple therapy with 5-FU. Steroids and testosterone were employed in both groups as mentioned above. If the 8 "fresh"

cases of inflammatory carcinoma are excluded from this tally, as well as the 4 induced deaths, and the 9 cases initially given 5-FU triple therapy, then the observed regression in advanced disseminated metastases from TP and MTX alone was 23/37 or 62% in Group I compared to 43/55 or 79% in Group II. The higher proportion of responses since 1962 could reflect the fresh effect of testosterone which had not previously been given to two-thirds of the Group II patients, whereas only three Group I patients had not received prior testosterone. Since the 62-79% response rate includes a number of incompletely treated cases classified as failures, the results suggested that four out of five cases of advanced breast carcinoma have the potential to respond to thio-TEPA and Methotrexate in combination when supported with androgens and steroids.

TABLE II  
*Initial Combination Chemotherapy*  
Objective Regression in Major Organ Sites of Metastases

	TP + MTX	TP + MTX + TESTO → CYT a/o FU
	40 Pts. (1959-1961)	73 Pts. (1962-1965)
Skin and subcut. tissues	13/18	14/19
Lung and pleura	8/15	15/26
CNS	5/8	8/11
Osseous	3/9	13/19 (CYT)
Hepatic	1/8	7/9* (FU)
Abdominal and generalized	5/10	2/5
Intraocular	1/2	3/4
"Inflammatory" breast	2/2	6/7
Total pts. response	25/40	59/73

\* 5-FU added in 9 hepatic pts. CYT instead of TP in 2 hepatic pts.

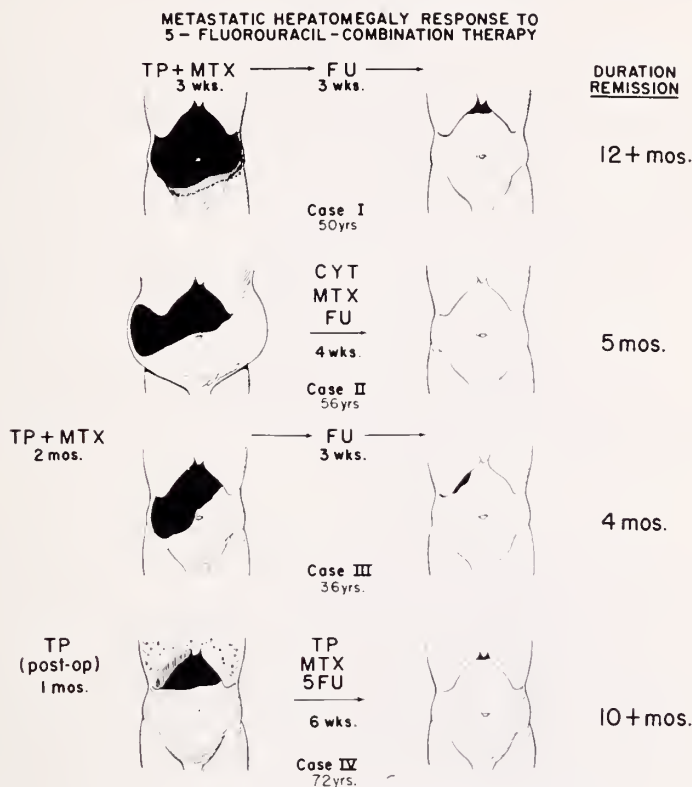
Note: All CNS, hepatic, diffuse osseous and abdominal cases given Prednisone. No responders showed accelerated realcification of osteolytic metastases. Radiotherapy to brain given for 7 of 19 CNS cases after first antifol effect.

#### *Character of Thio-TEPA-Methotrexate Regression*

The conspicuous feature of the TP + MTX effect was the rapid development of regression signs, often as early as 5-10 days after onset of chemotherapy. This was particularly evident in skin and subcutaneous metastases, pulmonary nodular infiltration and CNS signs. In some cases of severe CNS disability, (papilledema, paresis, aphasia, etc.) improvement was first manifest within 48 hours after onset of chemotherapy. The recently developed CNS signs usually responded more rapidly than the older deficits. Responsive skin and soft tissue lesions softened, darkened and shrunk as the antifol effect approached its height. Bone pain and pleural effusion also showed the first indications of response coincidental with the first bout of antifol toxicity.

Metastatic disease which had shown no response whatsoever by the third

week after starting the combination usually showed no response when the second course of MTX was given while on maintenance thio-TEPA. In this study a patient was not deemed to be TP-MTX resistant unless or until she had failed to respond to two courses of MTX. The results indicate retrospectively that when no symptomatic or objective response was observed after one full course of MTX to *minimal definite toxicity*, a significant regression should not have been expected after a second course of MTX. However, numerous



Note : These hepatomegaly cases given Testosterone & Prednisone

FIG. 1. Metastatic hepatomegaly regression after triple 5-fluorouracil combination chemotherapy in four successive cases. The Methotrexate-alkylating agent combination alone had been insufficient to consistently inhibit hepatic metastases prior to use of 5-fluorouracil.

cases which had shown partial regressions during the first bout of antifol therapy often showed further regression after the second or third course of MTX.

#### *Regression in Organ Metastatic Sites*

Table III summarizes the regressions observed in major sites of metastatic involvement in the 40 Group I patients given TP plus MTX and in the 73 Group II patients treated with the multiple regimen. An equally high incidence of responses was observed in skin and soft tissue metastases in both groups

(13-18; 14-19). Most of these regressions coincided with the appearance of Methotrexate antifol stomatitis. The longest sustained regression of diffuse subcutaneous metastases persisted for 10 months with four courses of MTX before relapse. The other responders developed resistant recurrence in 4-8 months despite intensive MTX and TP. Lung and pleural metastases (Figs. 2, 3) showed the same order of responsiveness as cutaneous and CNS metastases, i.e., 8-15 in Group I and 12-20 in Group II.

The proportion of TP + MTX responses in CNS metastatic disease was the same (5-8; 8-11) as in skin and subcutaneous metastases. Neurologic signs, including papilledema, ocular palsies, brain stem lesions, aphasias and paraplegias, responded with rapid dramatic objective improvement at the height of the antifol stomatitis phase. In general the more recent the onset of CNS signs, the more rapid was the regression of neurological deficits. All CNS cases

TABLE III  
*"Poor Risk" Category for Combination Chemotherapy*

---

Extensive x-ray therapy to bones
Diffuse osseous metastases
Impaired renal function
Marked anemia, hypoproteinemia
Protracted vomiting, diarrhea
Severe cachexia
Prolonged therapy:
I.V. fluids
Antibiotics
Steroids
Diuretics
Male risk > female risk
Old age over 65

---

which responded had extra-cranial metastatic disease which regressed simultaneously (Fig. 3) as the CNS signs subsided. Regressions were of shorter duration in those treated with chemotherapy alone (Table IV) than in those treated with chemotherapy followed by adjuvant cobalt therapy. Six of seven patients given non-localized cobalt radiation broadside to the brain through large lateral portals, remained in remission more than 6 months and survived more than 1 year, compared to only 3/11 similar responses to chemotherapy alone (Table IV). Nine of nineteen patients with CNS metastases survived more than one year on this therapy. Radiotherapy was usually commenced a few days after the first course of MTX had been completed, and completed shortly after the second course of MTX.

Chorio-retinal metastases in six patients were treated with TP + MTX. Four of these six showed regression and control of the chorio-retinal lesions for the duration of their survival. Two were later given Cytosan and one was given CYT and FU for extraocular recurrence.

The poor response in testosterone-resistant osseous metastases was evident by the observation that only 3 responses could be obtained among 9 Group I patients treated with TP & MTX. However, when androgens and steroids were initiated with the TP & MTX in "fresh" cases of diffuse bone disease a higher incidence (10/14) of response was obtained. Objective criteria for regression in bony metastases were difficult to assess quantitatively since neither series showed any evidence of accelerated recalcification of osteolytic metastases despite objective hematologic, functional and symptomatic signs of response.

### *Secondary Chemotherapy Responses*

Since 1962, 6 of 19 patients with diffuse osseous metastases who had shown only partial short-term responses to the TP + MTX regimen have responded with remissions of more than six months (Case 4) duration when Cytoxan replaced TP as the maintenance alkylating agent. This represented almost one-third of those presenting with diffuse osseous metastases. Among a larger group of 31 patients with skin, soft tissue and pulmonary metastases, Cytoxan induced regression in only five patients after failure or recurrence on TP + MTX.

Eighteen cases exclusive of those with metastatic hepatomegaly, were given Cytoxan plus 5-FU after failure of TP + MTX. Five of eighteen showed secondary responses to this combination, but none remained in remission more than four months. 5-FU was not employed alone in any patient during this study.

### *Triple Cytotoxic Therapy*

The usual poor prognosis of massive metastatic hepatomegaly was shown in the failure of seven of eight Group I patients to respond to TP, MTX and Prednisone. Because of these failures, 5-FU was added to the combination chemotherapy in 9 Group II cases of hepatic metastases, since 1962. All nine of these patients showed regression of liver metastases, seven developed an associated clinical remission, and four showed sustained remissions of more than 4 months duration (Fig. 1), 2 for more than one year. Some patients showed subsidence of jaundice and ascites. The detailed use of FU for metastatic hepatomegaly in these patients is discussed elsewhere (10-12).

### *Inflammatory Carcinoma*

Ten cases of so-called inflammatory carcinoma were treated with thio-TEPA and Methotrexate (Table V). Nine of ten showed marked and in some rapid regression of massive lesions involving the entire breast and axilla (Fig. 4). The tenth patient died a toxic death postoperatively (v.s.). Each case was treated with repeated courses of Methotrexate while on thio-TEPA maintenance. Seven already have survived in remission more than one year and four of these are in remission more than 2 years after onset of chemotherapy.

The combination chemotherapy appeared to suppress visceral or osseous dissemination, since such extensive regional neoplasms would have been ex-



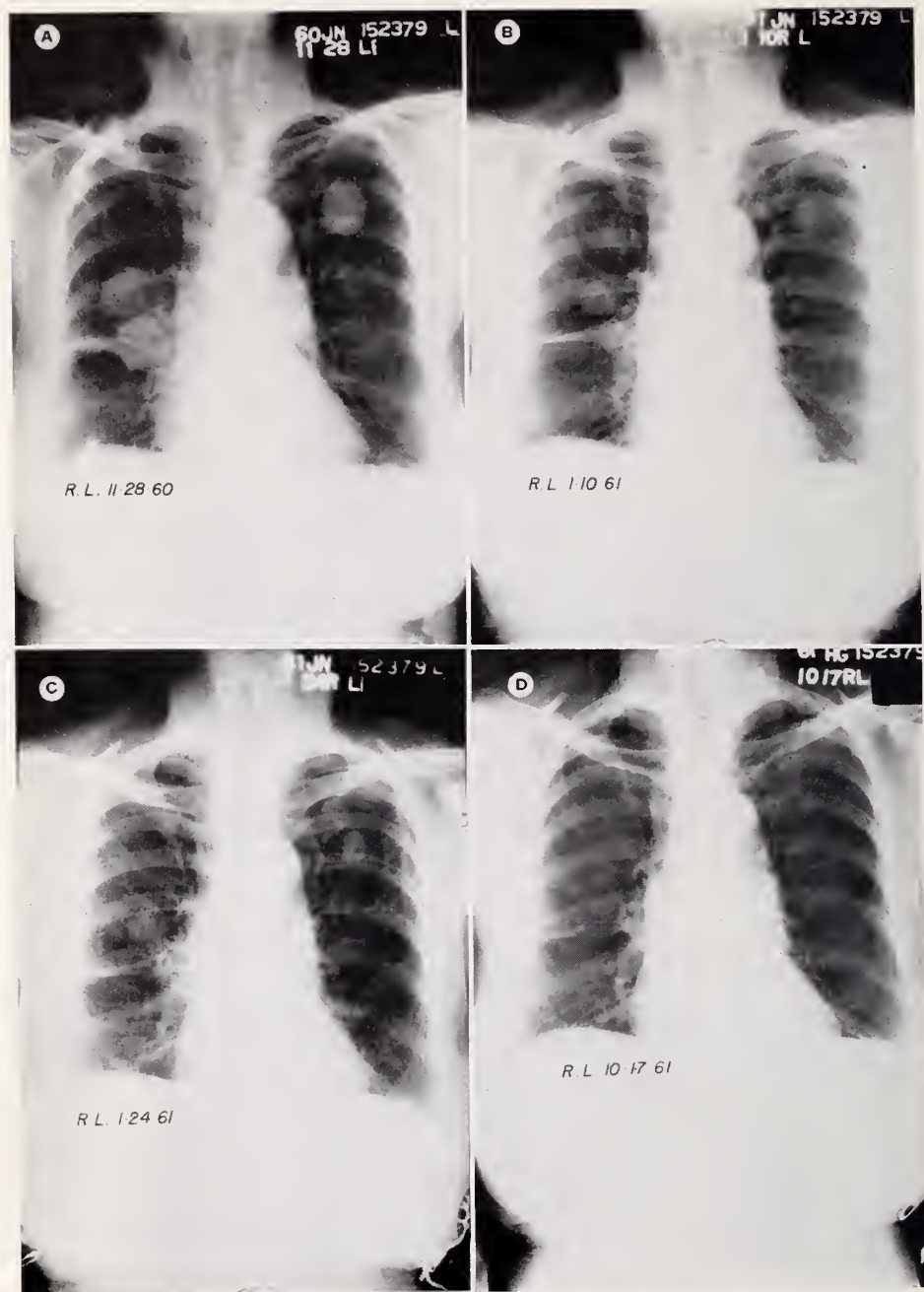


FIG. 2. Serial chest roentgenograms showing rapid regression of multiple pulmonary metastases after priming and maintenance thio-TEPA simultaneous with 2 courses of Methotrexate therapy (see case summary #1 for details).

pected to show gross metastatic spread within 4 to 6 months without chemotherapy. In one case, a single initial pulmonary metastasis which promptly disappeared coincident with regression of the primary lesion after chemotherapy, recurred with bilateral pulmonary dissemination 20 months later. These fresh metastases were TP-MTX resistant, but responded partially to secondary chemotherapy with Cytosan (Case 5). There was no indication that the repeated administration of the antimetabolite-alkylating agent combination supported with maintenance testosterone lowered the systemic resistance of patients to the regional "inflammatory" neoplasm.

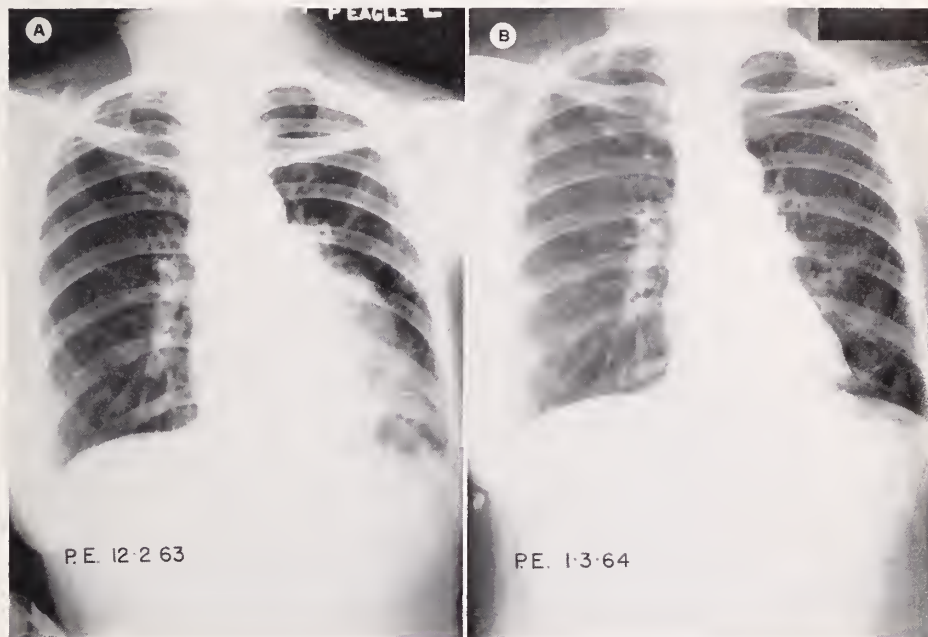


FIG. 3. Serial chest x-rays showing regression of pleural effusion and pulmonary infiltration at left lung base, within one month after TP-MTX chemotherapy. (See case #2 for details.)

#### DURATION OF REMISSION AND SURVIVAL

The relatively short duration of combination chemotherapy responses was indicated by a median regression of 6.6 months in Group I and slightly over 7 months in Group II. Half of the responders showed active recurrence of metastatic growth resistant to TP and MTX within 2 to 6 months after the onset of treatment. After exclusion of the cases of inflammatory carcinoma, 27% of all Group I and 39% of Group II remained in remission for more than 6 months. From 15-20% remained in remission for one year (excluding the nine cases of inflammatory carcinoma). The two year survival was less than 10% in Group I and will probably not exceed 15% in the Group II cases (see summary Table VI).



## RELATION OF AGE OR PREVIOUS THERAPY

Responses to TP + MTX therapy occurred without relation to the age or previous surgical therapy, post-op radiotherapy or radiation for recurrent disease. Numerous recurrences within previously radiated portals showed regression after TP + MTX therapy. Previous castration therapy, or ovarian radiation therapy appeared to reduce the likelihood of response by 15-20%. However, results were especially influenced in cases of diffuse osseous metastases resistant to testosterone. Such patients showed a relatively small number of TP + MTX chemotherapy responses compared to "fresh" bone cases not

TABLE IV  
*Combination Chemotherapy Results—Intracerebral Metastases*

Patient	Age	R.T.	Duration	
			Response (mos.)	Survival (mos.)
A.B.	30	0	3	6
C.H.	56	0	11+	11+
B.Z.	33	0	2	4
Z.R.	59	0	7	12+
F.G.	47	0	0	6
J.F.	50	0	2	8
P.E.	53	0	3	5
S.S.	49	0	0	1
N.S.	48	0	9	15+
E.W.	50	0	0	2
R.F.	66	0	0	3
P.F.	39	0	0	2
H.S.	48	+	8	13
T.B.	34	+	6	13
E.M.	50	+	15	33
P.W.	58	+	14	45
E.L.	51	+	8	12
D.L.	49	+	5	8
A.D.	44	+	11	17

Median Age: 48.5 yrs.

previously treated with testosterone. Since reviewing our results a prompt resort to Cytoxan therapy has been advocated in androgen-resistant bone metastases.

## REPRESENTATIVE CASES

*Case 1*

*Rapid Regression of Primary Lesion and Pulmonary Metastases After Thio-TEPA and Methotrexate Alone*

R. L. (MSH #152379), aged seventy-four years, refused mastectomy for a slowly enlarging mass in the right breast of one and one-half years' duration.

Needle biopsy of the mass, 7 x 10 cm, revealed adenocarcinoma. Chest x-ray showed large bilateral pulmonary metastases (Fig. 2). Oral Methotrexate, 7.5 mg per day for nine days was given to the point of minimal stomatitis, together with 60 mg of intramuscular thio-TEPA. As soon as the antifol stomatitis appeared, the patient noted marked reduction in the breast mass. Maintenance thio-TEPA was begun four weeks after these priming doses. A second course of Methotrexate was given five weeks after the first course. X-rays taken revealed marked reduction in the pulmonary metastases six weeks and eight weeks after initiating this combination therapy (Fig. 2). The primary lesion in the breast was no longer palpable at this time. The patient was maintained on thio-TEPA, 15 mg intramuscularly, every two or three weeks for ten

TABLE V  
*Results—"Inflammatory" Carcinoma*

Patient	Age	Onset Chemotherapy*	No. MTX Courses	Cobalt	Mastectomy
L.S.	55	6/62	8	Sep-63	Nov-63
J.M.	47	11/62	6	Jan-63	Feb-63
A.J.	45	10/63	3	Jan-64	Dec-63
R.S.	48	10/63	5	Oct-63 ovaries	—
E.B.	83	1/64	2	—	—
C.S.	55	1/64	2	Jan-64	Feb-63 left Feb-64 right
C.H.	56	5/64	3	May-63	—
M.G.	72	11/64	2	—	—
E.S.	78	12/64	4	—	—
A.E.	51	1/65	1	Post-adrenalectomy toxic death	—

\* All surviving June, 1965 except cases A.E. and E.B. (Lost to follow-up after nine months.)

months, with exhibition of a moderate steady leukopenia. A third and fourth course of Methotrexate was given six and eight months after the initial combination therapy. After ten months of this combined regimen, anemia and purpura developed in association with depression of white blood cells to 2,800 and platelets to 60,000/cu mm. Thio-TEPA was withdrawn, testosterone was initiated and a single transfusion was given. Recovery of peripheral blood was rapid within three weeks.

Chest x-ray one year after initiating combination chemotherapy showed virtually no evidence (Fig. 2) of the large pulmonary metastases previously seen. The breast lesion, which had regressed completely and remained under control for a year after starting therapy, now began to show progressive regrowth. The metastatic lesions showed no response to two months of Cytosan therapy. Massive estrogen therapy was then instituted, but after three months failed to prevent the development of extensive pulmonary metastases. She

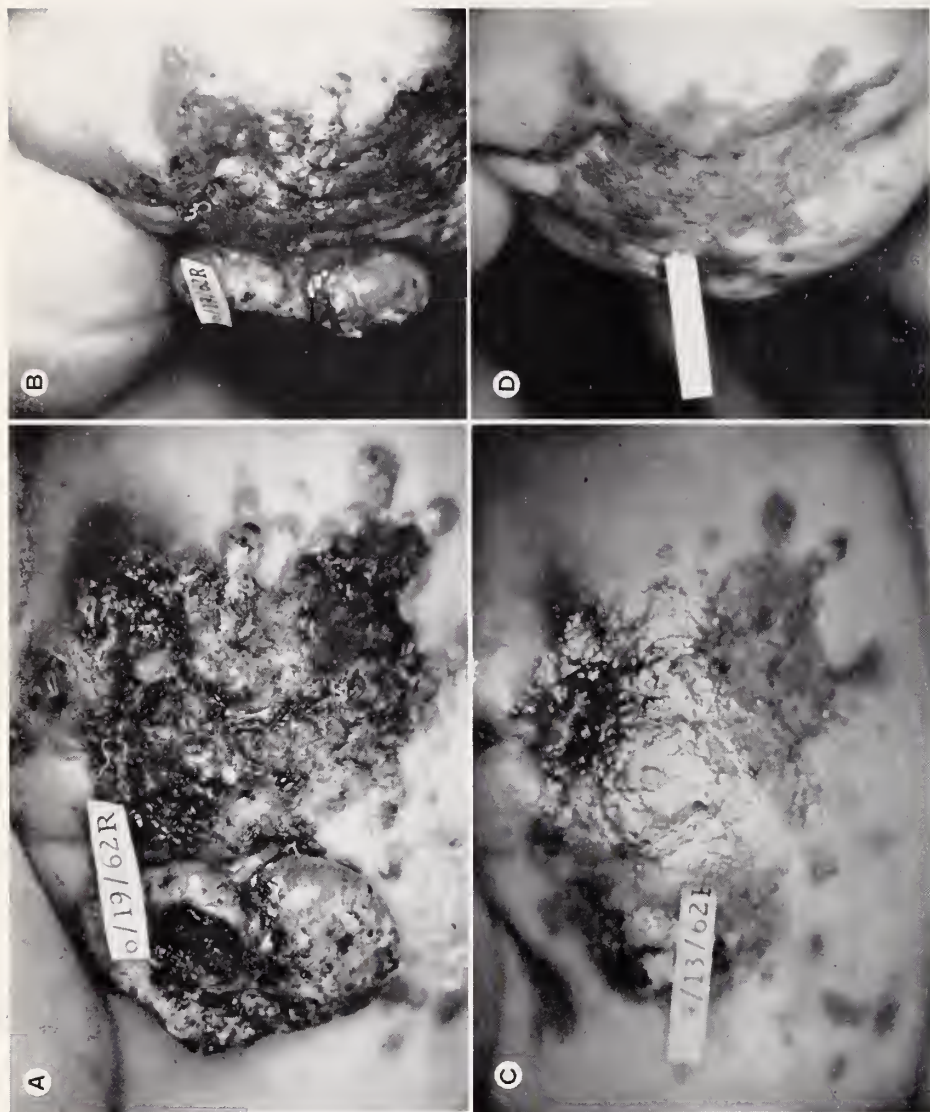


FIG. 4. Large, fungating ulcerating carcinoma with massive inflammatory components extending into axilla and right chest wall. Four courses of Methotrexate and thio-TEPA over a 4-month period resulted in marked shrinkage and flattening of major tumor masses and reduction in numerous nodular metastases on the chest wall (see case #3 for details).

was then admitted with cerebral metastases in a terminal state. Thio-TEPA and Methotrexate now given in combination with steroids and androgens, resulted in a dramatic transient recovery from an apparently moribund state. She died with progressive cerebral and pulmonary metastases, five weeks after this last four-fold trial of chemotherapy and hormone therapy.

### Case 2

#### *Simultaneous Rapid Regression of Pulmonary and CNS Metastases*

P. E. (MSH #237426). Radical mastectomy was performed on this 52-year-old female two years previous to onset of symptoms of intracranial metastases

TABLE VI  
*Results Combination Chemotherapy*

	TP + MTX	Multiple Regimen
	1959-1961	1962-1965
<i>Objective Regression</i>		
None.....	15	13
2-6 mos.....	10	30
6-12 mos.....	7	21
>1 yr.....	8	10
Total Pts....	40	73
<i>Median Regression (mos).</i>	6.6	7.0+
<i>Survival</i>		
>1 yr.....	8	25 (3)*
>2 yrs.....	4 (1)*	8 (3)*
Total Pts.....	40	73

\* Inflammatory carcinoma in parentheses.

in August, 1963. Progressive ataxia, headache, papilledema, aphasia, vomiting and partial paresis developed over a three month period before admission to the neurosurgical service at Mount Sinai Hospital. On December 1, 1963, she was started on combination oral Methotrexate, intramuscular thio-TEPA, 20 mg daily of oral prednisone and aqueous crystalline testosterone (Combination A). Within 48 hours after onset of chemotherapy there was a prompt improvement in the neurological disabilities. These resolved completely after the appearance of antifol stomatitis on December 6. On December 12 she was discharged in an ambulatory and neurologically normal state, for maintenance thio-TEPA and further treatment with Methotrexate. Complete regression of left pulmonary and pleural metastases was observed four weeks after onset of chemotherapy. A second course of Methotrexate was given on 12/28 and a third course on 1/26/64, while the thio-TEPA maintenance was administered at 15 mg every seven to ten days. On February 29, the patient complained of

some recurrence of CNS symptoms. Antifol stomatitis was induced on 3/2, but neurologic symptoms did not subside, though chest x-ray showed no recurrence. On 3/20 she was admitted to Mount Sinai Hospital for study. A brain scan showed "only one metastasis in the right frontal lobe confirmed by brachial angiogram." After development of papilledema and other signs of increased intracranial pressure, surgical exploration was performed but multiple metastases were found predominantly in the right frontal lobe and cerebellum. She died April 30, 1964, three weeks after exploration.

### *Case 3*

#### *Regression of Massive Inflammatory Carcinoma After Repeated TP + MTX Followed By Cobalt Therapy and Radical Mastectomy*

A 55-year-old spinster appeared with a large, fungating, ulcerated inflammatory carcinoma of the right breast, of several years duration (Fig. 4). This tumor mass infiltrated the entire right breast and axillary fold, but did not involve the supraclavicular fossa grossly. Surgical biopsies revealed infiltrating scirrhous carcinoma (Dr. S. Otani). Surgical consultant deemed the lesion unresectable in its presenting form. The patient showed severe cancerphobia, fear of surgery, profound mental depression and guilt over this neglected lesion. Menopause had occurred four years previously.

A course of combination chemotherapy with simultaneous TP and MTX was begun on June 19, 1962. The full priming dosage of 60 mg of TP was given, followed three weeks later by maintenance TP, 15 mg intramuscularly every seven to fourteen days sufficient to maintain a mild leukopenia. The first dosage of MTX in this "good-risk" patient consisted of 7.5 mg of MTX orally for four days followed by 10 mg for the subsequent three days, given simultaneously with the initial priming doses of TP. The typical antifol stomatitis appeared on the eighth day after starting the oral Methotrexate. At the height of this initial antifol reaction, when the white count was 3,200 cells per cu mm, the tumor mass began to shrink visibly in size. Three successive courses of Methotrexate were given on July 17, August 16 and September 2nd. The shrinkage of tumor masses was progressive and accompanied by gradual disappearance of the large fungating pedunculated tumor appendage without occurrence of any slough or significant bleeding (Fig. 4). The ulcerating lesions epithelized, the edema subsided, and satellite nodules in the axilla and axillary fold disappeared after the second course of Methotrexate.

Slight diffuse alopecia and minimal leukopenia was observed throughout the entire four months to TP + MTX therapy. The lowest hemoglobin was 12 Gm and the least white count was 3,200 without any accompanying purpura or thrombopenia. The alopecia subsided completely four weeks after stopping the fourth course of MTX. During the four months of chemotherapy, the patient was given much psychological support, resulting in her consent to a course of cobalt radiation therapy in October, and a radical mastectomy on December 20, 1962. Post-operative healing was excellent. She returned to work on mainte-



nance thio-TEPA and androgens. She was well until October, 1963, when pain developed on pronation and supination of the right forearm, together with a warm 4 x 6 cm fusiform swelling over the radius. X-ray examination showed an erosive metastatic bone lesion of the right radial head and proximal shaft. This regressed after cobalt therapy. She was again well until October, 1964, where there was recurrence of pain, swelling and warming at the previous lesion. She was again given Methotrexate to the point of stomatitis without effect on the bone lesion. Immediately after the stomatitis Cytosan, orally, was initiated. Within two weeks regression of the local signs of recurrent osseous disease occurred coincidental with recurrence of partial diffuse alopecia. Cytosan, 200 mg per day orally, for twenty days each month has been given since December, 1964. At the present time (June, 1965) her disease is in clinical remission without any sign of activity, 2½ years after onset of continuous chemotherapy. Constant leukopenia has been maintained, but anemia or thrombopenia never occurred.

#### Case 4

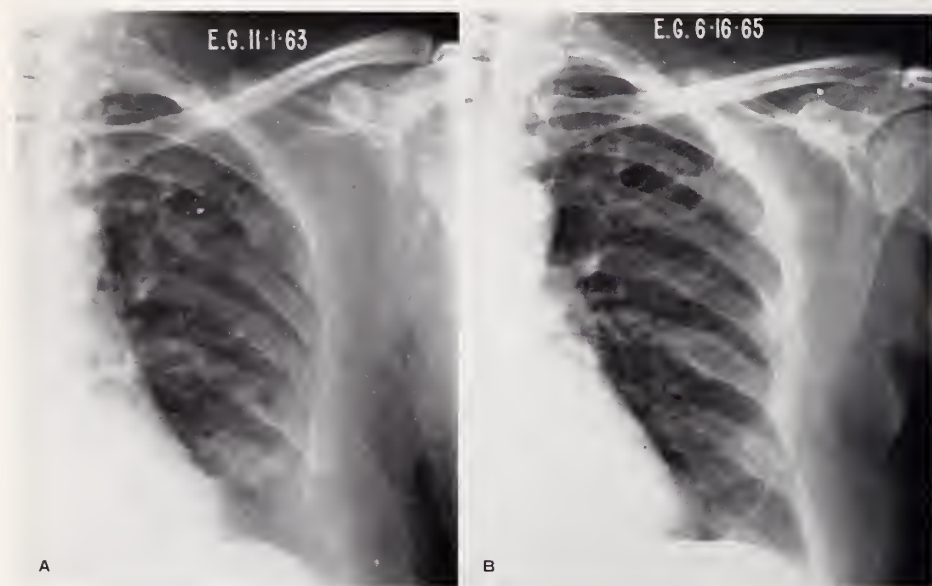
##### *Response of Diffuse Osteolytic Metastases to Cytosan After Inadequate Regression On TP, MTX, Androgens and Steroids*

E. G.: A 47-year-old patient first noted progressively severe disabling, diffuse bone pain in ribs, cervical neck, dorsal and lumbar regions in January, 1963. Multiple osteolytic lesions of the ribs, cervical, dorsal and lumbar spines with multiple rib fractures and major collapse of the fifth cervical vertebra and fourth lumbar vertebra were demonstrated in May, 1963. An open rib biopsy performed at another hospital showed metastatic carcinoma, but the primary site could not then be determined. A cervical collar and back brace were prescribed but she remained partially bed-ridden. Several inches in height were lost and progressive pain and disability continued. Total hysterectomy for fibroids had been performed six years previously.

On September 30, our initial examination now revealed a primary palpable tumor 3 x 3 cm in the left breast, plus signs of vertebral collapse, with marked limitation of motion of the cervical, dorsal and lumbar spine. A priming course of thio-TEPA plus aqueous crystalline testosterone, a "poor-risk" dosage of oral Methotrexate and small doses of oral Prednisone were administered simultaneously (Combination Schedule A). Antifol stomatitis appeared on October 26. By November 1, the breast lesion had virtually disappeared and her bone pain had markedly improved. To reduce the hazard of ambulation in the presence of several osteolytic lesions of the spine, Cobalt therapy to the lower lumbar spine through an 8 x 15 cm portal to a tumor dose of 3000 rads was given from November 9 to November 30. The thio-TEPA was continued on a maintenance schedule 15 mg every two weeks, androgens were continued with full masculinization and a second course of Methotrexate was given in December, 1963.

Bone pain showed further reduction. The primary breast lesion was no

longer detectable. From December to April, there was slight improvement in mobility, but bone pain continued. Moderate leukopenia was constantly maintained with thio-TEPA, but no anemia or thrombopenia was induced. Seven months after onset of combination therapy there was still no visible recalcification of the osteolytic metastases. In April, 1964 she was switched to oral Cytosin therapy, 150 mg daily for 20 days per month while masculinization was maintained on a reduced dosage of androgens. Within three to four weeks after starting the Cytosin, complete disappearance of bone pain and resumption of normal physical activity occurred. In July, 1964 three months after



FIGS. 5A AND B. Recalcification of rib lesions 1½ years after onset of combination chemotherapy, predominantly Cytosin effect (Case #4).

starting Cytosin, the osteolytic lesions began to show some degree of recalcification. Six months later sodium fluoride 25 mg q.i.d., p.o. was added to the therapeutic regimen. For 6 months thereafter, she was continued on cycles of Cytosin and continuous testosterone, sodium fluoride and 5 mg of prednisone daily. Vigorous health has been maintained with normal hemoglobin, fluctuating mild leukopenia and obvious shortened stature. No evidence of visceral or mammary recurrence is detectable 20 months after onset of chemotherapy. The bone lesions after 6 months of failure to respond to TP + MTX show (Fig. 5) recalcification deemed the result of Cytosin therapy. Serum alkaline phosphatase level, originally normal, are now at the borderline upper normal to slightly elevated range, while sedimentation and serum mucoprotein levels have returned to normal.



*Case 5**Response of CNS, Pulmonary and Soft Tissue Metastases After Recurrence On Radiotherapy, Estrogens and Adrenalectomy*

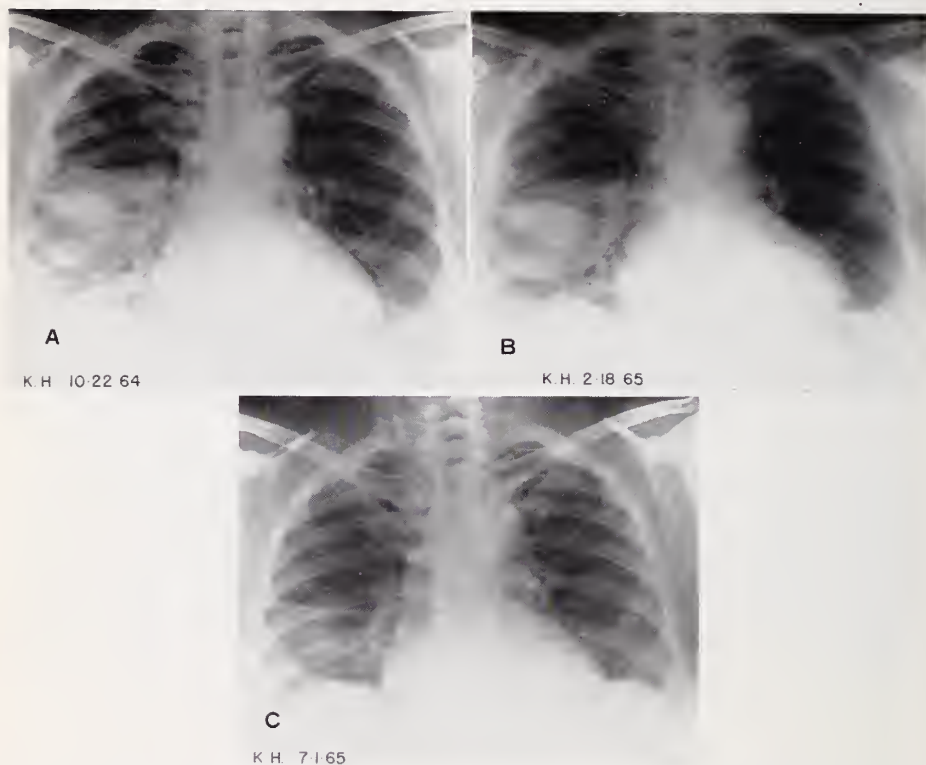
This 60-year-old patient had bilateral axillary metastases and a large Stage III right mammary carcinoma treated with four portal cobalt therapy in February, 1962. There was partial regression of palpable disease until November 1963, when recurrence of nodular chest wall disease within radiated ports was noted as well as axillary and supraclavicular adenopathy. Three months of estrogen therapy ended with further progressive metastatic growth. In April, 1964 a left eyelid ptosis was noted. Within two days she underwent bilateral adrenalectomy, but double vision occurred in June, accompanied by bilateral ocular palsies. Weakness of the left leg developed in July followed by lethargy and partial paresis, right pleural effusion with nodules and severe headaches with proptosis of right eye in August. On August 25 she was started on a combined course of thio-TEPA, Methotrexate and aqueous testosterone. No change was made in her steroid maintenance. As soon as the antifol stomatitis appeared after 2.5 mg of MTX, t.i.d. for six days, there was prompt and dramatic improvement in her neurological status and well-being. She was able to walk and vision was markedly improved. A second course of MTX was given four weeks later while on thio-TEPA and androgen maintenance. Further improvement in all areas ensued, including the nodular chest wall disease. A third course of Methotrexate was given January 7, 1965 and the fourth course on March 25. Now, one year after the onset of the TP + MTX combination therapy, she is in vigorous health with no neurologic disability and few residual signs of metastatic disease. The pleural nodules (scallop) and pleural effusion also regressed (Fig. 6A, B, C) during the year of combination chemotherapy. The TP + MTX regimen will be continued until signs of resistant recurrent metastases are seen. A course of Cytosan and/or 5-FU will be administered depending on the predominant site of the new organ metastases.

## DISCUSSION

The combination of TP + MTX for advanced breast carcinoma between 1959 and 1961 produced a rapid tumor inhibitory effect in about 60% of 40 Group I cases accompanied by acceptable safety under controlled clinical conditions after failure of the common methods of hormonal control. No comparable study of the use of an antimetabolite and an alkylating agent in breast carcinoma has come to our attention. Since 1961 (Group II) most new patients with life-threatening metastases were treated without waiting the three months necessary to observe the solo effect of Testosterone or ablative or castrations procedures per se. This more prompt resort to combination chemotherapy increased the incidence of induced regressions from about 60% in Group I to approximately 75-80% in Group II. This treatment of "fresh" cases of advanced metastases which resulted in 15-20% more remissions, appeared to have

permitted us to induce a "chemical castration" in a group which might otherwise have responded to the usual methods of castration and androgen therapy alone. The diverse inhibitory effects of thio-TEPA and Methotrexate on ovarian and adrenal function have been reviewed (9) but are not well known. They must be considered in evaluating these chemotherapy results.

Despite the high incidence (60%) of regression induced in Group I, only 37-39% remained in remission for 6 months or longer. The slightly earlier use



FIGS. 6A, B AND C. Gradual regression of pleural nodules and effusion during four courses of Methotrexate and thio-TEPA maintenance therapy (Case #5).

of chemotherapy in Group II did not appreciably increase the number who remained in remission 1½ years from onset of chemotherapy. Only 10-15% survived 18 months after onset of chemotherapy even when CYT + FU sequential therapy was added to the original TP + MTX combination.

The advanced, often pre-terminal character of the organ metastatic disease in most of our patients must be considered in comparing these results of combination chemotherapy with those of endocrine or ablative procedures. Although chemotherapy remissions were more prompt in developing (2-4 weeks) and were more frequent (60-80%) than the 15-20% hormonal responses which could have been expected, the median duration of chemotherapy control was

much shorter in duration than that obtained in the smaller number of hormonal-dependent tumors (6-7 mos. vs. 18-22 mos.). Combination chemotherapy thus does not represent an urgent primary form of therapy for cases of slow-growing, early metastatic disease in which adequate time appears to be available to observe the effects of oophorectomy, androgen therapy or other ablative procedures on metastases in non-vital organs.

As experience with the TP-MTX combination continued it became apparent that the 60-80% regression rate observed in skin, lung and CNS metastases could not be achieved in two categories of organ metastases, i.e., in diffuse osseous metastases and in metastatic hepatomegaly. Sequential chemotherapy with Cytosan and/or Fluorouracil was promptly initiated in such cases as soon as resistance or recurrence on TP-MTX was detected. This led to findings of practical clinical importance such as, the observation that Cytosan induced sustained remission in almost a third of patients with diffuse osseous metastases clinically resistant to TP + MTX + testosterone and Prednisone. A lack of cross-resistance between Cytosan and TP-MTX combinations has already been noted clinically in other neoplasms (13). However, for the psychologically-average patient we are reluctant to employ Cytosan as the initial alkylating agent due to its frequent G.I. side effects, severe alopecia and hemorrhagic cystitis. Alopecia has been extremely abrupt and complete whenever Cytosan was combined with Methotrexate.

The striking regression in metastatic hepatomegaly produced by adding 5-Fluorouracil to the TP + MTX combination since 1962 indicated a preferred role of 5-Fluorouracil in the treatment of hepatic metastases (10). An entero-hepatic excretion and concentration of 5-Fluorouracil in the upper G.I. tract may be related to this peculiar selectiveness. While our work was in progress, Dao and Grinberg at Roswell Park reported that 5-FU alone in sub-optimum doses safely induced regression of metastatic hepatomegaly in about  $\frac{1}{4}$  to  $\frac{1}{3}$  of a series of 45 breast carcinoma patients (12, 14). This appears to be a lower incidence of response than among the nine cases given triple chemotherapy. Details of the various aspects of three drug therapy (FU + MTX + TP or CYT) in our cases of metastatic hepatomegaly have been presented elsewhere (10).

The relative safety and the 60-80% incidence of short-term regressions suggest that combination cytotoxic chemotherapy with TP and MTX should be considered as an urgent method of treatment for patients with rapidly-growing, life-impairing disseminated metastases. This therapy offers the patient with CNS, diffuse pulmonary or other crucially placed metastases, a quick, albeit temporary, reversal of symptoms and disability. Our findings suggest that cases of cerebral, neurological or ophthalmic metastases should be treated as chemotherapeutic emergencies. The simultaneous response of CNS metastases and lung or skin metastases during the antifol effect was a striking clinical phenomenon. Preliminary experience suggests that the prompt treatment of CNS metastases with combination chemotherapy followed by broadside cobalt therapy offers the best chance for prolonged survival.

Regression of CNS metastases at the height of the antifol action suggests that systemic Methotrexate passes the blood brain barrier to some extent, perhaps with the aid of moderate steroid dosage. Regression of cerebral leukemia and diverse brain tumors after Methotrexate therapy (15) by the intrathecal route has been described. Massive steroid therapy alone induced only 3 short remissions in 45 cases of intracerebral breast metastases reported by Kofman (16). The role of steroids in potentiating the chemotherapy must also be considered, whether the effects are mediated through reduction of perimetastatic edema, improved blood supply or other mechanisms (16, 17).

The usual tendency of continuous thio-TEPA therapy to induce anemia, thrombopenia, purpura and bleeding appears to have been avoided by the hematostimulation from testosterone and the use of modest doses of steroids. Many patients showed remarkable hematologic tolerance to double drug combination in sequence, as a result of the androgen effect, at times bordering on an induced polycythemia. Since Gardner's (18) first paper on androgens and erythropoiesis others have also noted the excellent protection afforded patients on chemotherapy with androgen therapy (19, 20).

The daily examination of "poor-risk" patients during the first course of Methotrexate, was a *sine qua non* in order to avoid fatal overdosage after the first signs of an oncoming antifol effect. The severe systemic toxicity of Methotrexate (irreversible once fully established) could be prevented only by carefully individualizing the patient dosage according to clinical risk category and not according to weight. While the use of citrovorum factor may accelerate the recovery from any unexpected severe antifol state, it cannot block fatal antifol dosage after such has been given. However, the definite antifol "titration" endpoint and the availability of citrovorum factor make Methotrexate a more precisely effective, feasible and probably safer antimetabolite than 5-FU for initial combination chemotherapy. Each of three supportive measures (androgens, steroids and B12) appeared to play a role in the relatively low drug-induced mortality observed after combination chemotherapy. Continuous, relatively large doses of B12 do not counteract (21) the tumor inhibiting effect of antifols. In addition, B12 may prevent macrocytic anemia from developing (22) without altering the underlying folic acid deprivation state.

The patient's acceptance of the toxic and cosmetic effects from TP, MTX, and testosterone depends on the vigor, interest and psychological control manifested by the chemotherapist towards his patient. Good rapport, frequent blood counts and reliable communication during ambulatory antifol therapy is necessary for safe combination chemotherapy. The availability of inexpensive attractive wigs has made severe alopecia an acceptable side effect for most patients, particularly if the alopecia is gradual and partial during the first course of chemotherapy, at a time when clinical improvement usually becomes manifest. Patients who suffer oral ulceration and other upper G.I. symptoms will accept repeated courses of Methotrexate, if they achieve recognizable relief of symptoms or signs of cancer.

Our study suggests, but does not prove, that thio-TEPA synergizes the



clinical effectiveness of Methotrexate. Methotrexate alone induced 30% objective regressions in two independent studies on breast cancer patients by Wright (3) *et al.* in 1959 and by Nevinny *et al.* (20) in 1965. In both series the response rate of skin and subcutaneous metastases was strikingly similar. Since we observed a 60% response rate at the height of the first antifol effect, it appears that Methotrexate is a more potent factor than TP. Although there were no concurrent single drug controls in our study, the incidence of 60-80% regressions obtained with TP + MTX is distinctly greater than expected from any single drug therapy. Such a high incidence of rapid regressions in life-threatening organ metastases has not been reported from Methotrexate alone. However, an occasional report on thio-TEPA and 5-Fluorouracil mentions almost comparable response rates in less advanced metastatic disease. In

TABLE VII  
*Tentative Selection of Agents for Combination Chemotherapy*

A. *Hormone Resistant Metastases*

Basic Therapy = Thio-TEPA + Testosterone

Supplementary Agents:

Soft Tissue	MTX
Soft Tissue and Fibrosis	MTX + Steroids
CNS	MTX + Steroids
Lung, Nodular	MTX
Hepatic	FU + Steroids → MTX and/or CYT
Osseous	MTX → Cytosan
Lung, Lymphangitic	MTX → CYT → FU

B. *TP + MTX Resistant*

FU and/or Cytosan

C. *"Inflammatory" Carcinoma*

TP + MTX + Testo (+ steroids): after 2 months, radiotherapy started; if no distant metastases after six months offer surgery. Then resume maintenance TP + MTX. Later CYT and/or FU.

crucially-ill patients the use of modest steroid dosage with the TP + MTX combination appeared to potentiate the anti-tumor effect while the androgens and B12 enhanced the tolerance to the antimetabolite and alkylating agent.

Since chemotherapy responses may far outnumber the hormone dependent responders, the practicing clinician may wonder how the four chemotherapeutic agents and the supportive measures fit into the general management of advanced breast carcinoma. For slow-growing metastatic disease in non-vital organs, a three-month trial of endocrine control appears advisable before resorting to combination chemotherapy. However, the more advanced and rapid the spread of metastases, the more likely is combination chemotherapy to offer a temporary but worthwhile palliation not obtainable by conventional radiation, ablative or hormonal measures. A scheme of the interdigitation of the various modalities discussed in this paper, is tentatively offered in Table VII. The responsible physician must be committed to avoid homeopathic underdosage, toxic overdosage or any transitory, haphazard, ambivalent trial of these

difficult and relatively unfamiliar agents to obtain the maximum benefits of cytotoxic chemotherapy.

#### SUMMARY

Simultaneous combination chemotherapy with the alkylating agent thio-TEPA and the antimetabolite Methotrexate was relatively safe in 113 cases of advanced breast carcinoma provided dosage was adjusted to the clinical risk category of each patient. TP + MTX induced short-term objective regression in 60% of cases with skin and subcutaneous, regional pulmonary and CNS metastases, but in few cases of diffuse osseous or hepatic metastases. When TP and MTX were combined with Testosterone and Prednisone, in previously fresh non-hormone treated cases, three-fourths of a large series showed objective regression and clinical remission, usually of 3-9 months duration. Triple therapy with 5-Fluorouracil added to the combination cytotoxic regimen resulted in regression of heretofore pre-terminal hepatic metastases. Secondary remissions in bone metastases were induced by Cytosan therapy after failure of thio-TEPA and MTX. A small series of inflammatory carcinomas responded to the TP and MTX regimen without any evidence of breakdown of host immunity on long-term maintenance chemotherapy. Despite simultaneous TP and MTX combinations and sequential therapy with Cytosan and 5-Fluorouracil, only 10-15% of all cases remained in remission after 18 months. Although the more numerous regressions after combination chemotherapy were more transient than usual remissions of hormone or ablative therapy, they provided worthwhile temporary effective control of rapidly-growing, life-threatening organ metastases.

#### REFERENCES

1. Bateman, J. C., and Carlton, N. N.: The Role of Chemotherapy in the Treatment of Breast Cancer, *Surgery*, 47: 895, 1960.
2. Schoenbach, E. B., Colsky, J., and Greenspan, E. M.: Observations on the Effects of the Folic Acid Antagonists, Aminopterin and Amethopterin, in Patients with Advanced Neoplasms, *Cancer*, 5: 2101, 1952.
3. Wright, J. C., Cobb, J. P., Golomb, F. M., Gumport, S. L., Lyall, D., and Safadi, D.: Chemotherapy of Disseminated Carcinoma of the Breast. *Ann. Surg.* 150: 2, 221, 1959.
4. Ivy, H. C.: Treatment of Breast Cancer with 5-Fluorouracil. *Ann. Int. Med.*, 57: 598, 1962.
5. Stoll, B. A., and Matar, V. H.: Cyclophosphoramide in Advanced Breast Cancer. *Brit. Med. J.*, 2: 283, 1961.
6. Freckman, H. A., Fry, H. L., Mendez, F. L. and Maurer, E. R.: Chlorambucil-Prednisolone Therapy for Disseminated Breast Carcinoma. *J.A.M.A.*, 189: 23, 1964.
7. Skipper, H. E., Chapman, J. B., and Bell, M.: The Anti-Leukemia Action of Combinations of Certain Known Anti-Leukemia Agents. *Cancer Research*, 11: 109, 1951.
8. Goldin, A., Greenspan, E. M., and Schoenbach, E. B.: Studies on the Mechanism of Chemotherapeutic Agents in Cancer; VI. Synergistic (Additive) Action of Drugs on a Transplantable Leukemia in Mice. *Cancer*, 5: 153, 1952.
9. Greenspan, E. M., Fieber, M., Lesnick, G. and Edelman, S.: Response of Advanced Breast Carcinoma to the Combination of the Anti-Metabolite Methotrexate and the Alkylating Agent, thio-TEPA. *J. Mt. Sinai Hosp.*, 30: 246, 1963.



10. Greenspan, E. M.: Regression of Metastatic Hepatomegaly from Mammary Carcinoma; Cytotoxic Combination Chemotherapy with 5-Fluorouracil. *New York J. Med.* 64: 2442, 1964.
11. Greenspan, E. M.: Combinations of Methotrexate, thio-TEPA and 5-Fluorouracil in Advanced Breast Carcinoma, *Proc. Am. Ass. Canc. Res.*, 5: 23, 1961.
12. Dao, T. L., and Grinberg, R.: Fluorinated Pyrimidines in Treatment of Breast Cancer Patient with Liver Metastases. *Cancer Chemotherapy Rep.*, 27: 71, 1963.
13. Greenspan, E. M.: Angiosarcoma Responsive to Cyclophosphamide after Failure of the Combination of thio-TEPA and Methotrexate. *Cancer Chemotherapy Rep.*, 11: 147, 1961.
14. Grinberg, R. and Nemoto, T.: Abstract #93, Treatment of Advanced Cancer of the Breast with 5-Fluorouracil. *Proc. Am. Ass. Can. Res.*, 6: 24, 1965.
15. Newton, Jr., W. A., and Sayers, M. P.: Intrathecal Methotrexate Therapy of Brain Tumors of Childhood. *Pro. Am. Ass. Can. Res. Abstract #190*, 6: 48, 1965.
16. Kofman, S., Garvin, J. S., Nagamini, D., and Taylor, S. G.: Treatment of Cerebral Metastases from Breast Carcinoma with Prednisone. *J.A.M.A.*, 1963: 1473, 1957.
17. Ruderman, N. B., and Hall, T. C.: Use of Glucocorticoids in the Palliative Treatment of Metastatic Brain Tumors. *Cancer*, Vol. 18; No. 3, 1965.
18. Gardner, F. H., and Pringle, J. C., Jr.: Androgens and Erythropoiesis. I. Preliminary Clinical Observations. *Arch. Int. Med.* 107: 846-862, 1961.
19. Brodsky, I., Dennis, L. H., and Kahn, S. B.: Bone Marrow Protection With Testosterone During Cancer Chemotherapy. *Clin. Res.*, 11: 399, 1963.
20. Nevimny, H. B., Hall, T. C. and Haines, C. R.: Comparison of Testosterone Propionate (TP) and Methotrexate (MTX) In the Treatment of Breast Cancer. *Pro. Am. Ass. Can. Res. Abstract #189*, 6: 48, 1965.
21. Greenspan, E. M., and Goldin, A.: Personal observations.
22. Alperin, J. B.: Vitman B<sub>12</sub> for Folic Acid Deficiency. *Am. J. Clin. Nutr.*, 15: 117, 1964.

## Addicting Drugs: Narcotics and Non-Narcotics

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The prevailing image of the "dope addict" is that of a poor, uneducated Negro or Puerto Rican from the slums of the metropolitan area, who occasionally makes the headlines through hold-ups or robberies. He makes the endless revolving door cycle of jails and detoxifications in specialized hospitals, only to start the entire process all over again upon his return to the community. No doubt, a large number of addicts fit that description. But there is an increasing awareness of the existence of another addict population. These addicts do not purchase their drugs on the black market at exorbitant prices, with the police in constant pursuit. These addicts belong to the middle or upper economic and social strata, and misuse certain drugs prescribed for them bona fide by their physician. Not only are the commonly prescribed narcotics used, but also drugs which in the past have rarely been suspected of addicting properties, like hypnotics, "diet pills" (amphetamines), medication to "calm the nerves" (tranquilizers), etc. It must be stated immediately that these drugs per se are very valuable, and that the daily practice of medicine without them, be it in the office or the hospital, would be set back several decades. Like with any potent drugs, there exist indications and contraindications for their proper use; the desired therapeutic effects must be weighed not only against the possible toxic effects, side-effects, allergies, etc., but also their addiction liability.

Sometimes the physician is shocked to find that a patient of his has been an addict without his knowledge; sometimes this patient has become addicted through the physician's inadvertence. Although not every eventuality can be foreseen, it is advisable not to prescribe unnecessary quantities of such drugs without the safeguard of periodic visits, or even better to prescribe only the amount which will carry the patient only till the time of the next visit. It is advisable to make sure that such prescriptions cannot be renewed without the physician's knowledge and consent. This kind of medication should be administered only as long as the target symptoms persist.

Despite these precautions it is possible that the patient may become addicted. Such patients will usually be quite insistent that they be given certain drugs in definite amounts, and they display an uncommon knowledge of drugs with similar action. They become anxious, when questioned about possible addiction, since they fear discovery. Some addicts "make the rounds" of physicians to receive the addicting medication by prescription.

It should not be forgotten though, that despite the enormous increase in the amount of drugs prescribed and consumed, only a relatively small number of persons become addicted. It is still impossible to predict what sort of person-

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ality tends to become addicted, and who, on the other hand, can use these drugs safely over a long period of time in relatively large quantities.

With some chagrin it must finally be said, that the medical profession, together with nurses and pharmacists, constitute the single largest occupational category of addicts, since access to these drugs is so easy for them.

#### CLASSIFICATION OF ADDICTING DRUGS

The medical profession is becoming increasingly aware of the problems of addiction to narcotics and non-narcotics, and of the necessity to treat those addicted within their community rather than sending them off to some distant specialized hospital.\*

It is generally accepted that addiction is the outgrowth of serious psychological problems, which require psychiatric treatment. The immediate task, however, once the diagnosis is established, is to withdraw the patient from the addicting drug. Proper management of this phase may be of great importance in establishing the right tone for the future therapeutic relation.

The following classification (see Table I) reflects in a general way the outlines of Isbell (1), and Kielholz and Battegay (2), but also includes some newer drugs and substances, used by addicts. This outline has been found useful and practical in handling the problems of withdrawal. It has also facilitated teaching the practical problems of addiction to general practitioners as well as to psychiatric attending and resident staffs.

The chief criterion of addiction is the presence of dependence, physical and psychological. Physical dependence implies an altered physiology brought about by repeated, prolonged and continued administration of certain drugs. The abrupt discontinuation of this administration will give rise to a self-limited illness called the abstinence or withdrawal syndrome.

The opiates and the synthetic compounds with similar action ("opioids") give rise to withdrawal symptoms of marked irritability and autonomic dysfunction upon withdrawal of the implicated drug. Addiction to hypnotics (barbiturates and drugs with similar properties) and the "minor" tranquilizers manifests itself by convulsions and delirium (usually with paranoid trends) during withdrawal.

The above named two large categories have in common the fact, that treatment, although not impossible on an outpatient basis (3), should preferably be conducted in a hospital setting. The hospital, preferably a psychiatric ward, which provides close supervision and assures control of possible contraband, also gives greater comfort and safety to the patient. The treating physician can rely better upon the resident and nursing staff for frequent follow-up of the patient's condition and prompt action in case of emergency.

Within each of these categories exists an interchangeability of pharmacological properties not only recognized by the addict for the purpose of con-

\* See, for example, the Report of the Subcommittee on Narcotics Addiction of the Medical Society of the County of New York in *New York Medicine*, p. 46G-46L, January 20, 1965.

tinuing the process of addiction, but also for the treatment of withdrawal symptoms. For practical purposes, withdrawal from opiates and opioids is treated with decreasing doses of methadone, while secobarbital or pentobarbital in decreasing doses are used in the second group (4).

TABLE I

*Classification of Addicting Drugs (Modified after Isbell)*


---

CLASS I. DRUGS CAUSING BOTH PSYCHOLOGICAL AND PHYSICAL DEPENDENCE  
THEREFORE REQUIRING WITHDRAWAL TREATMENT

*Subclass A.* Opiates and opioids (CNS irritability and autonomic dysfunction on withdrawal)

1. Opium and its preparations [laudanum, paregoric, morphine, Pantopon, codeine, heroin, hydromorphanone (Dilaudid), dihydrocodeinone (Hycodan), oxycodone (Percodan)]
2. Morphinan group: Racemorphan (Dromoran), levorphan (Levo-dromoran)
3. Benzomorphan: Phenazocine (Prinadol)
4. Meperidine group: meperidine (Demerol), alphaprodine (Nisentil), anileridine (Leritine), piminidone (Alvodine)
5. Methadone group: methadone (Dolophine, Amidone). (The narcotic antagonists nalorphine and levallorphan are not addicting.)

*Subclass B.* Hypnotics and "minor" tranquilizers.\* (Convulsions and/or delirium on withdrawal)

1. Barbiturates
2. Chloral hydrate
3. Paraldehyde
4. Glutethimide (Doriden), methypylon (Noludar)
5. Ethchlorvynol (Placidyl), ethinamate (Valmid)
6. Meprobamate (Equanil, Miltown, Deprol)
7. Chlordiazepoxide (Librium), diazepam (Valium)
8. Alcohol

CLASS II. DRUGS CAUSING PSYCHOLOGICAL, BUT NOT PHYSICAL DEPENDENCE,  
THEREFORE NOT REQUIRING WITHDRAWAL TREATMENT

1. Marijuana (Indian hemp, hashish)
  2. Cocaine
  3. Amphetamines
  4. Sedatives and tranquilizers: bromides, reserpine, phenothiazines (chlorpromazine etc.)
  5. Hallucinogens (peyote, mescaline, LSD, morning glory seeds)
  6. Inhalants (glue, gasoline, ether, amyl nitrate)
  7. Antidepressants [imipramine (Tofranil), amitriptyline (Elavil), methylphenidate (Ritalin)]
- 

\* See the statement prepared by the AMA Committee on Alcoholism and Addiction, "Dependence on Barbiturates and Other Sedative Drugs," for a more complete list (J.A.M.A., 193: 107, 1965).

Although all of the addicting drugs create psychological dependence, only the above named groups create physical dependence. Drugs, which create psychological dependence exclusively, will not give rise to withdrawal symptoms, and there is no need for specific treatment of this phase of addiction in such patients. Therefore, the withdrawal of these drugs can be immediate and complete.

This group, in a general way, includes some stimulants, antidepressants, tranquilizers, as well as substances used sporadically for "kicks" (hallucinogens, glue, etc.). This does not imply that the patient will not complain of anxiety, depression, tension or insomnia upon withdrawal, but these symptoms will be treated as they should be in any psychiatric illness.

#### CONCLUSIONS

From the perusal of the table, the following conclusions may be drawn.

1. *The general symptomatology of the particular addiction.* Addicts of the Subclass A (opiates and opioids) are usually subdued, passive and withdrawn, while under the influence of drugs. Addicts of Subclass B (hypnotics, "minor" tranquilizers, etc.) appear drunk, show poor judgement and may become unpredictably aggressive, features which are well known in regard to alcohol, but much less so in relation to the other drugs of this Subclass.

2. *Characteristics of withdrawal symptoms.* It can be anticipated that patients addicted to drugs in Subclass A will have withdrawal symptoms characterized by CNS irritability and autonomic dysfunction, while those addicted to drugs in Subclass B may have convulsions and delirium (usually with paranoid trends).

3. *Need for treatment of withdrawal.* Drugs in Class II do not produce withdrawal symptoms, therefore no specific treatment is required. All drugs in Class I produce withdrawal symptoms, which should be treated in a hospital setting rather than at home or on an outpatient basis (this is especially true of Subclass B).

4. *Method of treatment.* Drugs in Subclass A can be interchanged with other drugs within the same subclass to withdraw the patient by diminishing doses of the drug; methadone, which can be given by mouth, is the drug of choice. The same principle applies to drugs in Subclass B, which can be used interchangeably within that subclass to withdraw the patient by diminishing the dosage of the drug; secobarbital or pentobarbital are the drugs of choice.

#### REFERENCES

1. Isbell, H.: The Pharmacology of the Opiates and Similar Addiction-producing Drugs. *Proc. Royal Soc. Med.*, 53: 925, 1960.
2. Kielholz, P. and Battegay, R.: The Treatment of Drug Addicts in Switzerland. *Compr. Psych.*, 4: 225, 1963.
3. Mason, P.: Management of Narcotic Addiction. In: *Psychosomatic Medicine*, eds., Nodine, J. H., and Moyer, J. H. Philadelphia: Lea & Febiger, 1962, pp. 845-849.
4. Blachly, P. H.: Procedure for Withdrawal of Barbiturates. *Am. J. Psych.*, 120: 894, 1964.



# The Role of Indicator Dilution Curves in Cardiovascular Studies

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The indicator dilution technique (1, 2) has become an integral part of present day methodology for the study of the cardiovascular system. The indicators employed have included such dyes as indocyanine green, Evans blue and Coumassie blue, ascorbic acid, inhaled hydrogen, hydrogenated saline, radioactive indicators such as krypton, iodinated albumin and alkyl iodides, cold saline and inhaled nitrous oxide. The various radiopaque dyes used in angiocardiology in reality constitute another variety of indicators employed for registration of dilution curves.

These varied modalities have been utilized primarily for the determination of cardiac output and regional blood flows, for the detection and localization of right to left and left to right intracardiac and extracardiac shunts, for determination of the blood volume between the point of injection and the sampling site and for the detection and localization of valvular insufficiency. The major purpose of this report is to illustrate the manner in which indocyanine green and ascorbic acid curves may be utilized to study intra and extra-cardiac shunts. The other indicators mentioned above will be discussed only briefly. The contributions of Wood, Swan and their collaborators (3-6) and Braunwald, Morrow and co-workers (7-10) have lain the groundwork for many of these studies. The methods and materials employed in this laboratory have been previously described (11-13).

## GENERAL PRINCIPLES

The basic concepts of indicator dilution curves in the normal subject and those with left to right and right to left shunts are illustrated in Figures 1-5. The injection site is the anatomic point at which the indocyanine green is introduced into the circulatory system. The sampling site is the area from which an indicator dilution curve is inscribed. In Figure 1, the indicator is injected into the right side of the heart and sampled from a systemic artery. In the normal subject, the bolus of dye passes through the right and left sides of the heart in series. The characteristics of this normal curve are well known, with a rapid upstroke after a normal appearance time. As the indicator passes the sampling point, the concentration falls nearly to the baseline. The recircula-

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tion curve is generally apparent. In subjects with a left to right shunt downstream to the injection site, a portion of the bolus of dye passes through the lungs and thence directly to the periphery; another portion recirculates within the lungs, and arrives at the periphery late, resulting in a break on the downstroke of the primary curve. In patients with a right to left shunt downstream to the injection site, a typical double-humped curve results. A portion of the bolus of dye bypasses the lungs to reach the peripheral arterial sampling site early. Another portion of the bolus circulates through the lungs to arrive at the

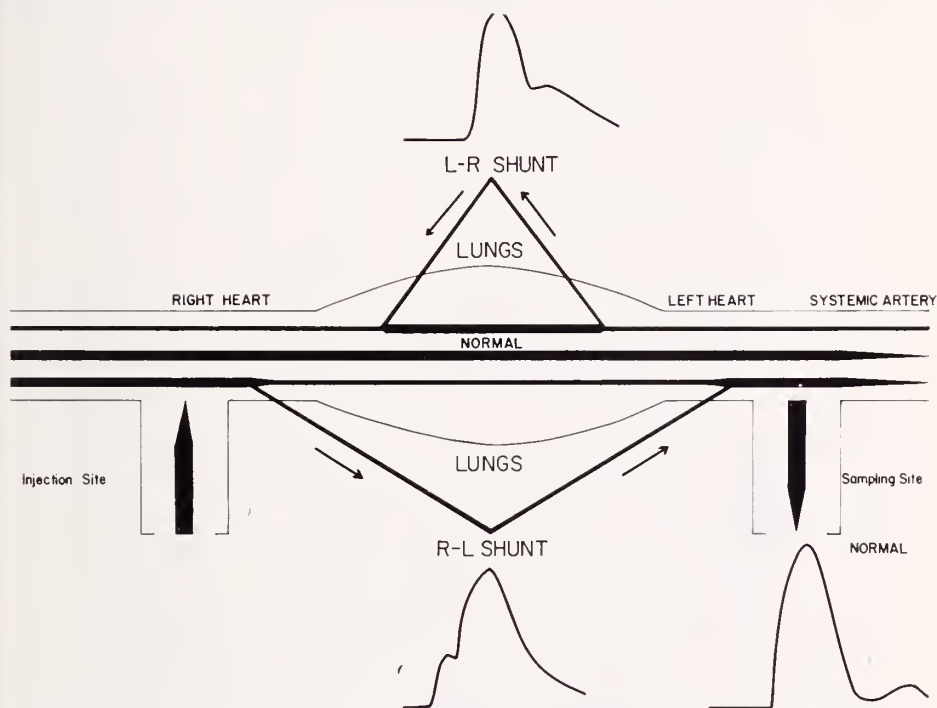


FIG. 1. Diagram of three possible circulatory pathways after a right heart injection site with peripheral arterial sampling. The curves illustrate the normal state, a left to right and a right to left shunt.

periphery at a later, but normal time, resulting in the typical appearance of the indicator curve. Multiple consecutive dye injections into the right side of the heart serve to localize the site of right to left shunting. For example, a double-humped curve with an early appearance time (interval from the moment of dye injection to the time the dye first appears in the systemic artery) from the right ventricle, but not from the pulmonary artery, pinpoints the right ventricle as the source of the right to left shunt.

Localization of the site of a left to right shunt is not possible by the technique of injection into the right heart with systemic arterial sampling. For example, injection into the pulmonary artery, right ventricle and right atrium with systemic arterial sampling will result in similar curves in the presence of a patent

ductus arteriosus, an interventricular septal defect or an interatrial septal defect. Localization of the left to right shunt is illustrated in Figures 2-5. These techniques consist either of constant injection and variable sampling site techniques, or constant sampling and variable injection sites techniques.

The constant injection variable sampling site approach was first described by Braunwald *et al.* (9) (Fig. 2), and Wood *et al.* (6) (Fig. 3). In the former method, the dye injection site is usually a peripheral vein. The chambers of the right heart serve as the variable sampling sites. As illustrated, in an inter-

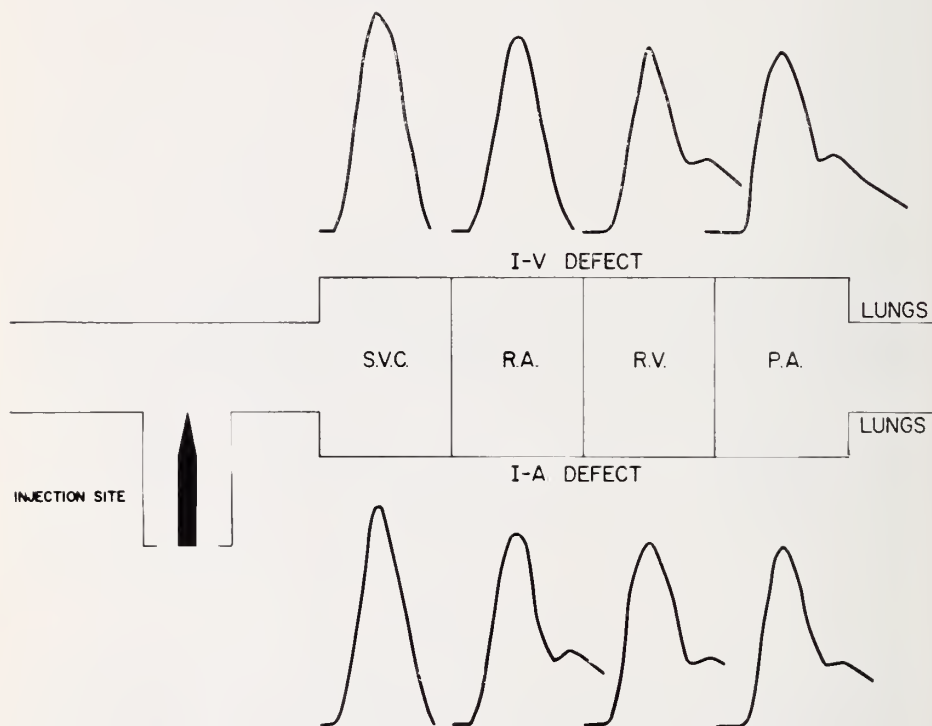


FIG. 2. Constant upstream peripheral venous injection site and variable downstream right heart sampling site. See text.

ventricular septal defect, the superior vena cava and right atrial curves are normal, but the downstroke of the right ventricular curve is interrupted by the dye shunted from the left to the right ventricle. In an interatrial defect, interruption of the downstroke is first noted in the right atrial curve as the sampling site is moved progressively downstream. An even more sophisticated approach is that employed by Wood *et al.* (6) (Fig. 3). The injection site is located downstream to the varied sampling sites. In an interventricular septal defect, dye injection into a pulmonary artery with right atrial or superior vena cava sampling is characterized by a long appearance time since the indicator must circulate from the pulmonary artery through the entire circulatory system before

appearing at the sampling site. On the other hand, if a right ventricular sampling site is utilized, the appearance time is considerably shorter, of the order of 2 or 3 seconds or less, since the indicator traverses only a short pathway before detection, i.e., from pulmonary artery to pulmonary vein to left atrium and ventricle and back to the right ventricle. Progressive movement downstream of the sampling site thus serves to localize the site of the left to right shunting. Two intracardiac catheters are utilized for this method.

The constant sampling site, variable injection site technique may also be utilized to detect and localize left to right shunts, as described first by Braun-

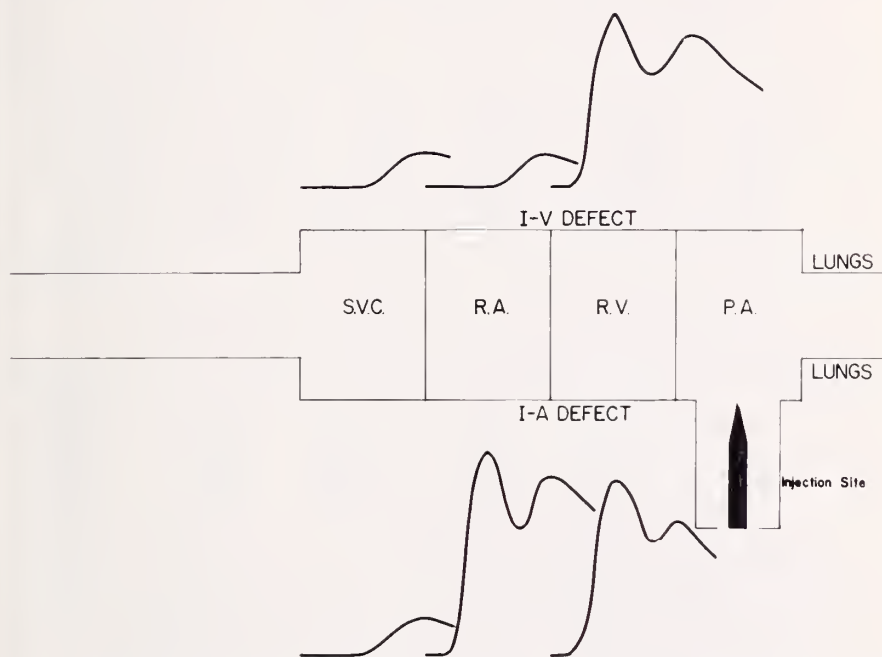


FIG. 3. Constant downstream pulmonary artery injection site and variable upstream right heart sampling site. See text.

wald, *et al.* (8) (Fig. 4). A systemic artery may service as the sampling site in this method. If the injector site is downstream to the site of the left to right shunt, a normal systemic arterial curve is obtained. If the injection site is at or upstream to the shunt site, interruption of the downstroke of the systemic arterial curve will occur. These curves are illustrated in Figure 4 for a left to right shunt at the ventricular or pulmonary artery levels. A variation of the two catheter right heart sampling technique (6) may also be employed to localize left to right shunts (Fig. 5). The sampling site is kept constant, for example, in the pulmonary artery, while the left heart injection site is varied. If the injection site is downstream to the left to right shunt, the interval from dye injection to its appearance in the pulmonary artery is normally prolonged,

perhaps 8-10-12 seconds. If the injection site is at or upstream to the left to right shunt site, the dye appearance time is foreshortened to perhaps 2-4 seconds.

In general, it has been our experience that left to right shunts can be detected and localized most decisively by utilization of the early appearance time approach (Figs. 3 and 5). The interruption of the downstroke technique (Figs. 2 and 4) may on occasion result in less positive identification of left to right shunts. The application of the above principles will be illustrated by indicator

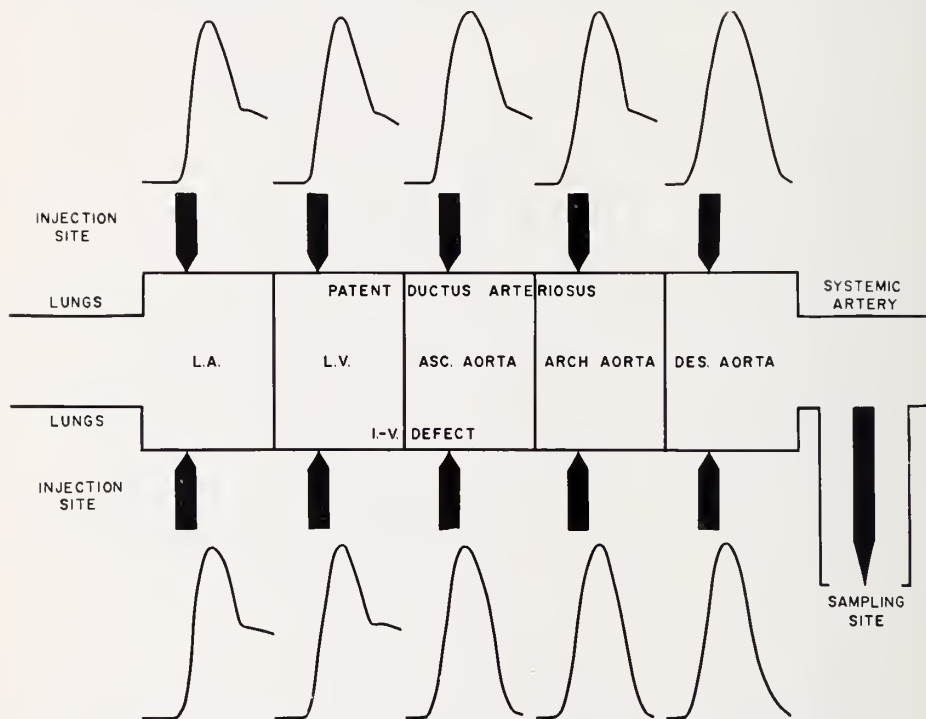


FIG. 4. Constant downstream sampling site with variable left heart upstream injection site. See text.

dilution curves with indocyanine green and ascorbic acid in varied types of congenital heart disease. The dye dilution curves were recorded on an eight channel photographic recorder (Electronics for Medicine), utilizing a Gilford densitometer and a Harvard constant infusion-withdrawal apparatus (11-13). Blood removed for dye curve inscription was re-infused at completion of inscription of the indicator curve. The technique for ascorbate curve inscription has been described previously (10, 14).

#### RESULTS AND DISCUSSION

Indicator dilution curves in a normal child are shown in Figure 6. To the left, the injection site is the pulmonary artery, the sampling site, the femoral

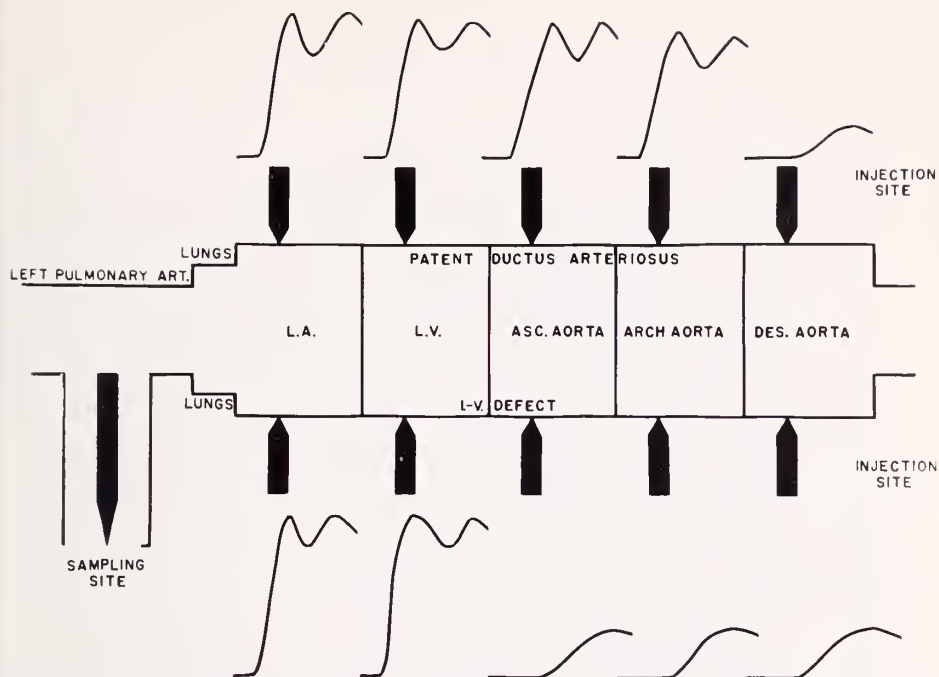
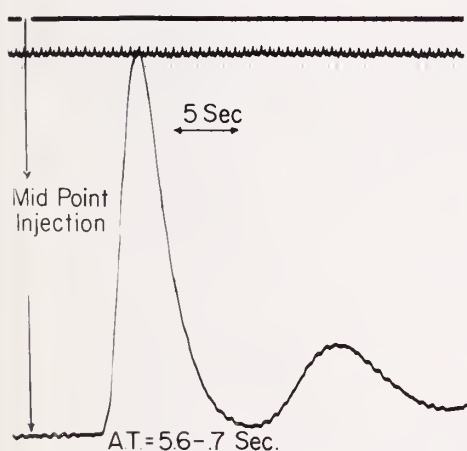


Fig. 5. Constant upstream sampling site with variable left heart downstream injection site. See text.

M Hes. NI Heart  
12-15-60

RPA to RFA (G-6-25)



L. Bra Vein to R.P.A. (G-6-25)

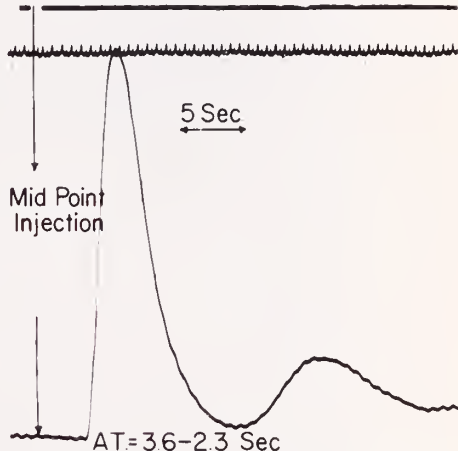


Fig. 6. Indocyanine green dilution curves in a normal child. The curve to the left is from the right pulmonary artery to the right femoral artery; that to the right is from the left brachial vein to the right pulmonary artery. The 0.7 sec. and 2.3 sec. time periods are subtracted to correct for the dead space volumes of the respective sampling systems.

S.Tay. Normal 1/5/63

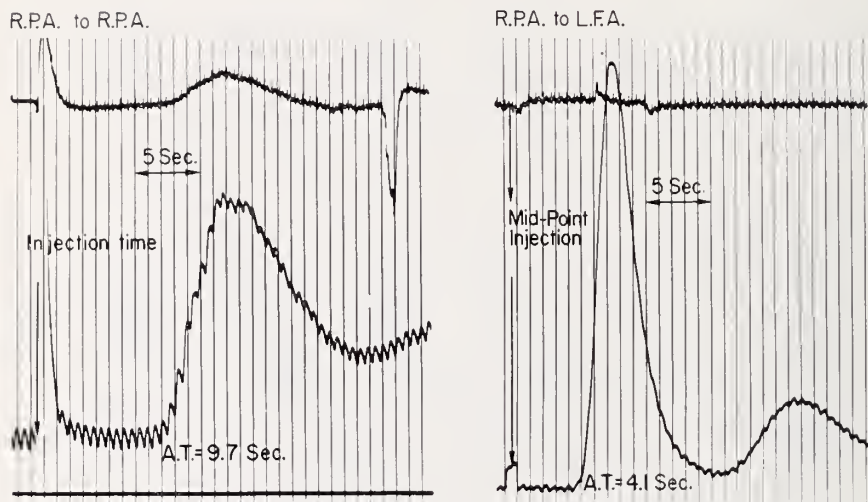


FIG. 7. Ascorbic acid and indocyanine green indicator dilution curves in a normal child. In the former curve the injection and sampling site is the pulmonary artery. The first deflection is caused by the ascorbate injection, the second by total body recirculation of ascorbic acid.

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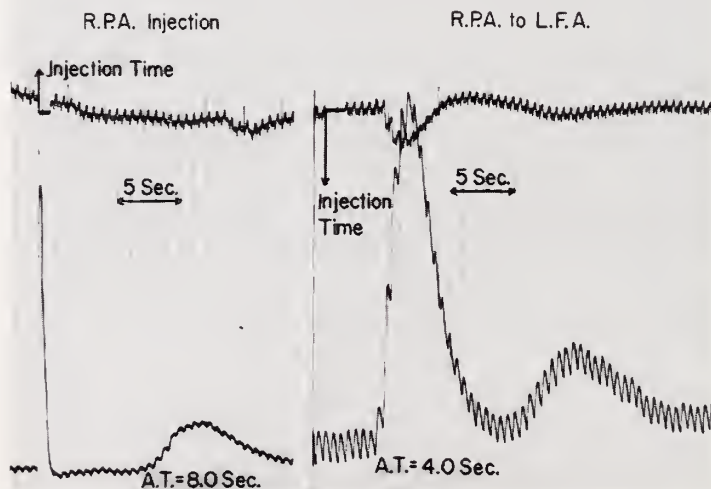


FIG. 8. Ascorbate dilution curves in a patient with congenital aortic valve disease. In the curve to the left the injection and sampling site is the pulmonary artery; in the curve to the right, the ascorbate is injected into the pulmonary artery and sampled from the femoral artery.



artery. To the right, the injection site is a peripheral brachial vein, the sampling site, a pulmonary artery. 0.7 sec. and 2.3 sec. refer to the dead space sampling delays of the arterial needle plus the connecting tubing plus the densitometer volume and to the volume of the cardiac catheter plus the other de-

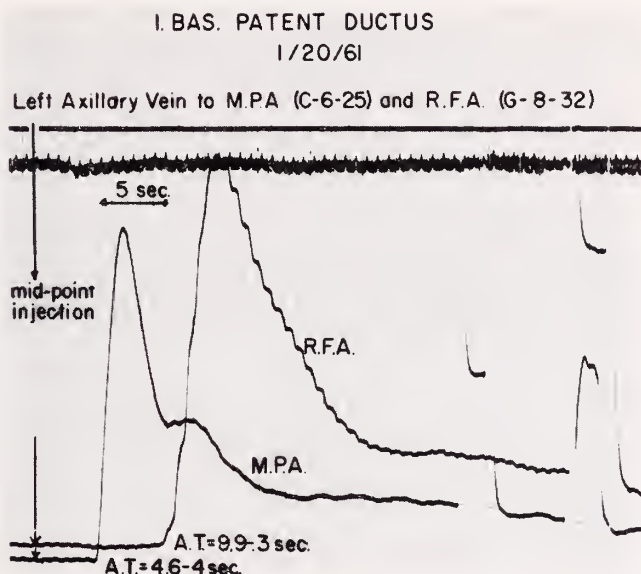


Fig. 9. Peripheral venous dye injection with pulmonary and femoral arterial sampling. The downstroke break on the former curve is more evident and denotes the presence of a left to right shunt, site undetermined.

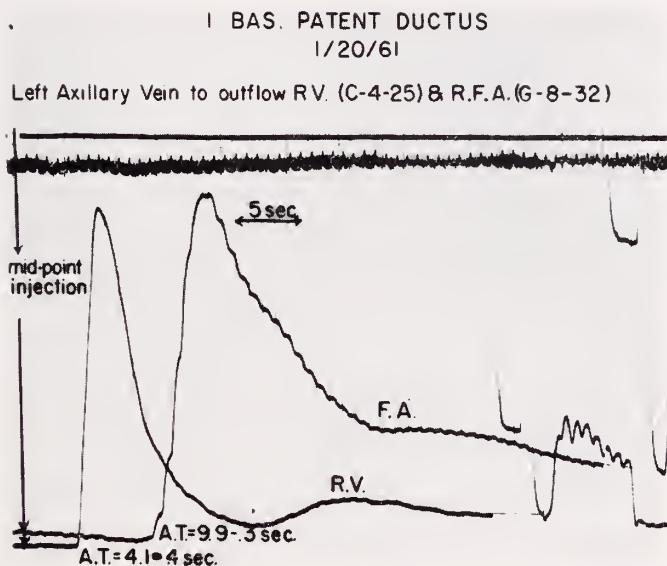


Fig. 10. Same patient as in Fig. 9. The absence of a break on the downstroke of the right ventricular curve localized the shunt to distal to the pulmonary valve.

## L. Bra. Patent Ductus Arteriosus

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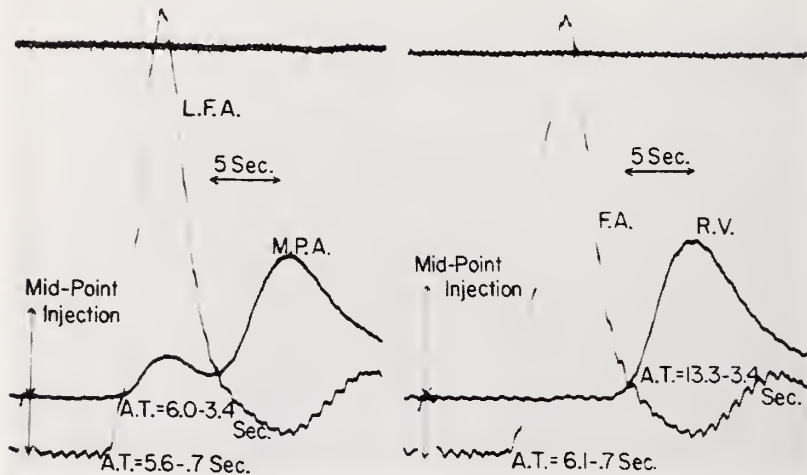
R.P.A. to M.P.A.(G-6-5-0)  
and L.F.A.(C-4-4-0)R.P.A. to R.V.(G-6-5-0)  
and L.F.A.(C-4-4-0)

Fig. 11. Constant pulmonary artery injection site with variable right heart sampling site. The early appearance time in the main pulmonary artery upstream to the injection site, together with the normally delayed right ventricular appearance time localizes the left to right shunt to distal to the pulmonary valve.

## L. Bra. Patent Ductus Arteriosus

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M.P.A. to M.P.A.

M.P.A. to M.P.A.

R.V. to R.V.

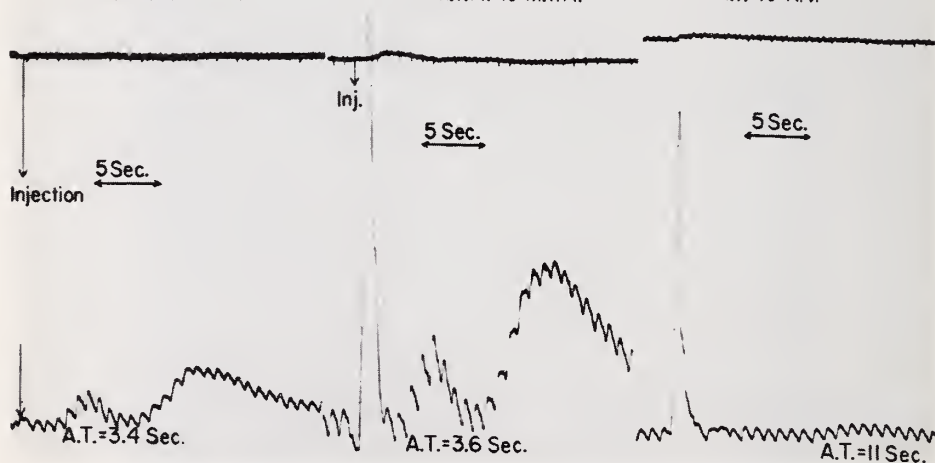


Fig. 12. Same patient as Fig. 11. Pulmonary artery injection and sampling sites during ascorbate injection reveal an early appearance time in contrast to the prolonged appearance time after right ventricular injection. Diagnosis verified at surgery.

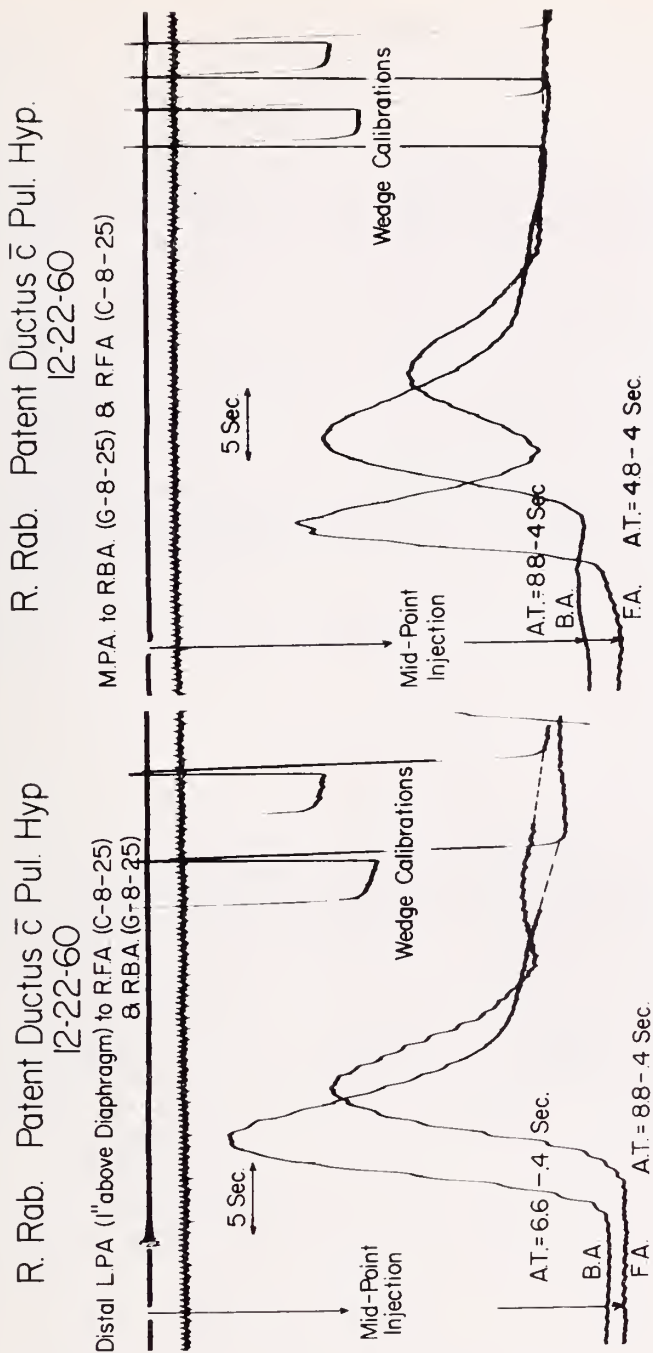


FIG. 13. Localization of the site of the right to left shunt in a patient with patent ductus arteriosus, pulmonary hypertension and reversal of the shunt. Distal left pulmonary artery injection results in a relatively normal femoral arterial curve in contrast to the double-peaked short appearance time femoral artery curve after main pulmonary artery injection.

## E.Lan. Patent Ductus Arteriosus

9/11/63

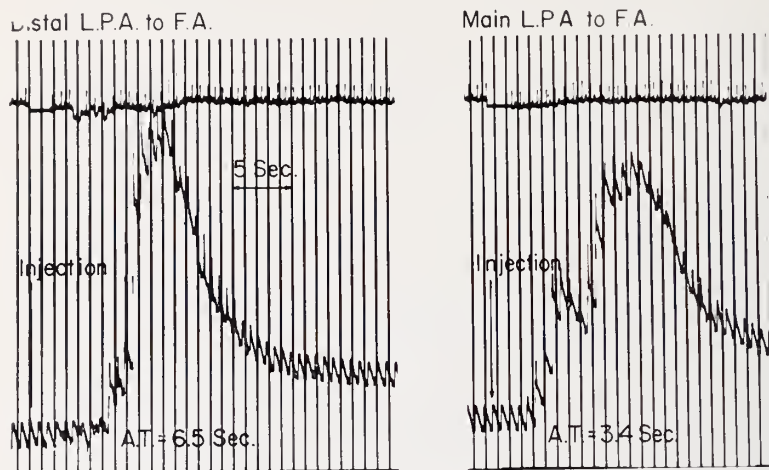


FIG. 14. Another patient with patent ductus arteriosus and shunt reversal, employing ascorbate as the indicator. The curve to the left (injection into the distal left pulmonary artery) is characterized by a longer appearance time than after main left pulmonary artery injection. The latter curve is also double-peaked.

## J. Bla. I.V. Defect

6/28/61

L.P.A. to R.V. (C-7-5-0) and R.B.A. (G-5-4-0) L.P.A. to R.A. (C-7-5-0) and R.B.A. (G-5-4-0)

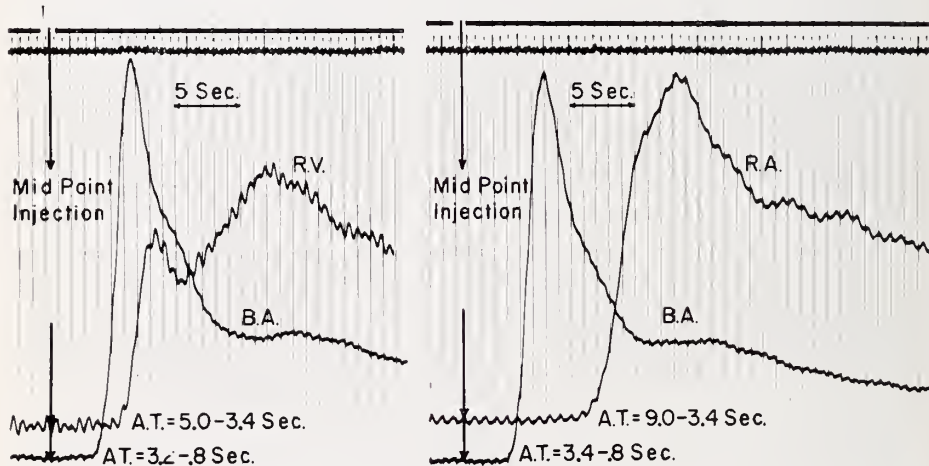


FIG. 15. Localization of an interventricular septal defect. The injection site in both curves is the left pulmonary artery. The right ventricular appearance time is shortened (1.6 sec.) in contrast to the prolonged right atrial appearance time (5.6 sec.) localizing the left to right shunt to distal to the tricuspid valve.

## D. Nov. I. V. Defect

6/14/62

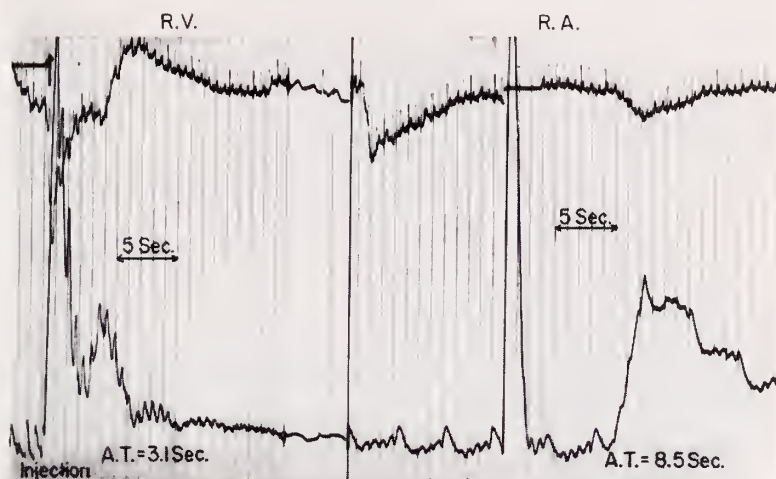


FIG. 16. Use of ascorbate curves to detect and localize a left to right shunt at the ventricular level. The shunt is distal to the tricuspid valve, with an early right ventricular appearance time and a normal right atrial appearance time.

## T. Hill. I.-V. Defect &amp; Pulmonary Hypertension

10/4/60

R.P.A. to R.F.A. (G-6-32)

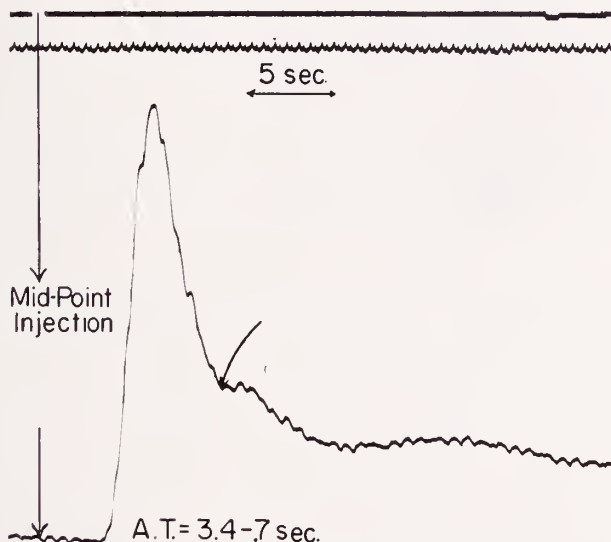


FIG. 17. Pulmonary artery injection and femoral arterial sampling via indocyanine green. The upstroke is normal; there is a break on the downstroke.

laying volumes respectively. Both curves are normal. The normal curves in Figure 7 follow use of ascorbic acid and indocyanine green respectively. The latter is similar to the curves in Figure 6. The former has an initial deflection due to the ascorbate injection; the second deflection, after a delay of 9.7 seconds, is caused by total body ascorbate recirculation in the absence of a left to right shunt. The large spikes superimposed on the curve baseline are characteristic of ascorbate curves. A similar indicator dilution curve is shown to the left in Figure 8. Total body ascorbate recirculation totals 8 seconds. To the right, ascorbate has been injected into the pulmonary artery with femoral

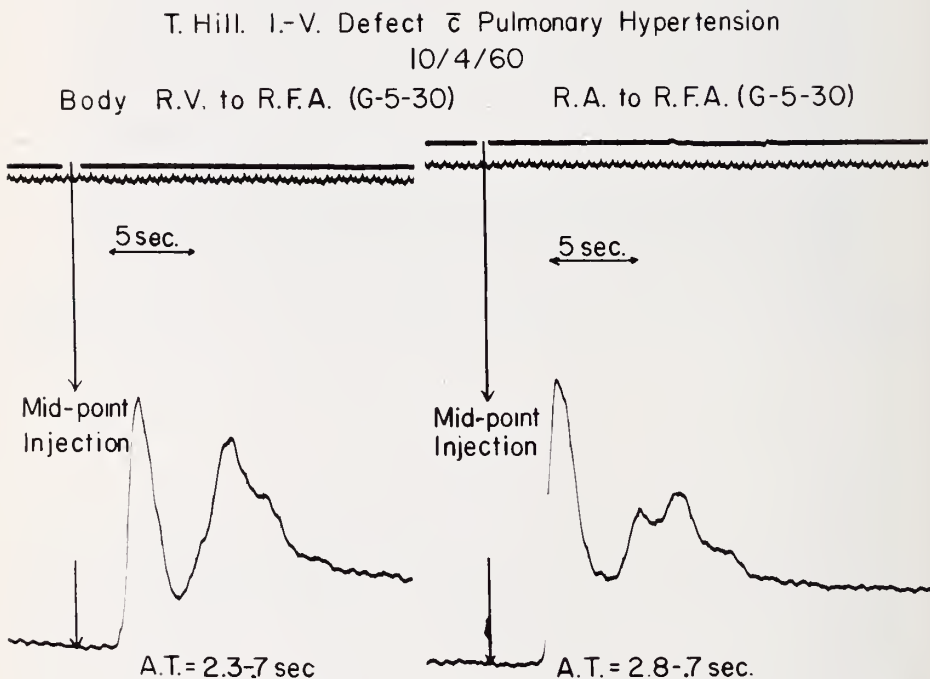


FIG. 18. Same patient as Fig. 17. The right ventricular and atrial appearance times are shorter than after pulmonary artery injection and the curve is double-humped. This is diagnostic of a right to left shunt at the ventricular level.

arterial detection via a Teflon coated platinum wire inserted into a 18-T Courmand needle. The curve contour is very similar to that of a normal indocyanine green curve, despite the presence of hemodynamically insignificant congenital aortic stenosis and insufficiency.

Detection and localization of a left to right shunt caused by a patent ductus arteriosus are shown in Figures 9-10, by the constant injection site variable sampling site technique. Peripheral venous indocyanine green injection with pulmonary and systemic arterial sampling reveals a break on the downstroke of both curves indicating a left to right shunt at or between the injection and sampling sites. However, sampling at the right ventricular site fails to reveal a downstroke break, localizing the shunt site to the aorta and pulmo-



nary artery, rather than to an intracardiac site. An alternative approach to the diagnosis of a patent ductus arteriosus is illustrated in Figure 11, again employing the constant injection but variable sampling site technique. Pulmonary artery injection with pulmonary artery sampling reveals a left to right shunt at this level but not the right ventricular level as evidenced by the 2.6 second appearance time in the former, but 9.9 sec. appearance time in the right ventricle. Ascorbate curves may be employed for the same purpose (Fig. 12). Pulmonary artery injection and sampling reveals an appearance time of ap-

## TET. FALLOT

J. Hei. #1527 3-25-65

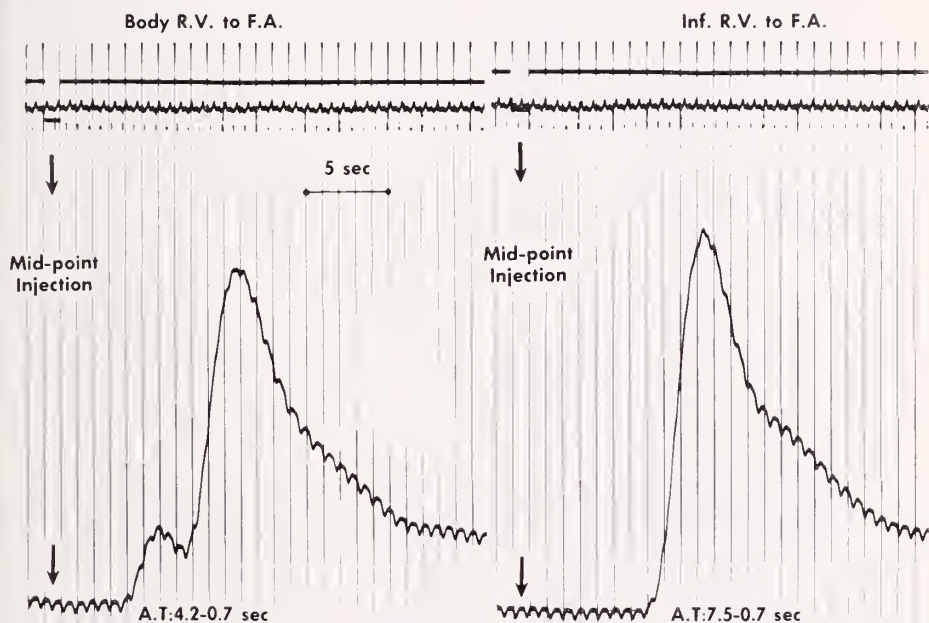


FIG. 19. Patient with a Tetralogy of Fallot syndrome. A right to left shunt with indocyanine green is evident only after injection into the body (but not the infundibulum) of the right ventricle.

proximately 3.5 seconds. On the other hand, right ventricular injection and sampling reveal a much longer total body recirculation time of 11 sec., localizing the shunt to downstream to the pulmonary valve. The data in Figure 13 illustrates the use of dye curves to localize a right to left shunt in a patient with a patent ductus arteriosus (surgically verified) and severe pulmonary hypertension with reversal of the shunt. Dye injection in the distal left pulmonary artery beyond the origin of the ductus produces normal appearance times in both the femoral and brachial arteries. Injection in the main pulmonary artery is accompanied by a normal brachial artery appearance time, but an early femoral artery appearance time. These data are pathognomonic of a

E. Fle. Tet. Fallot

2/1/63

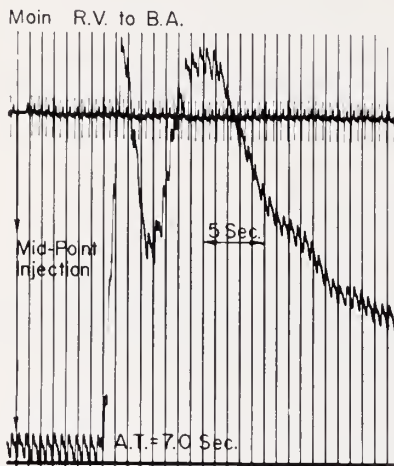


FIG. 20. Patient with Tetralogy of Fallot. A double-humped curve (ascorbate) is evident after right ventricular injection and brachial arterial sampling.

## ACYANOTIC TET.

J. Yat. #1513 3-15-65

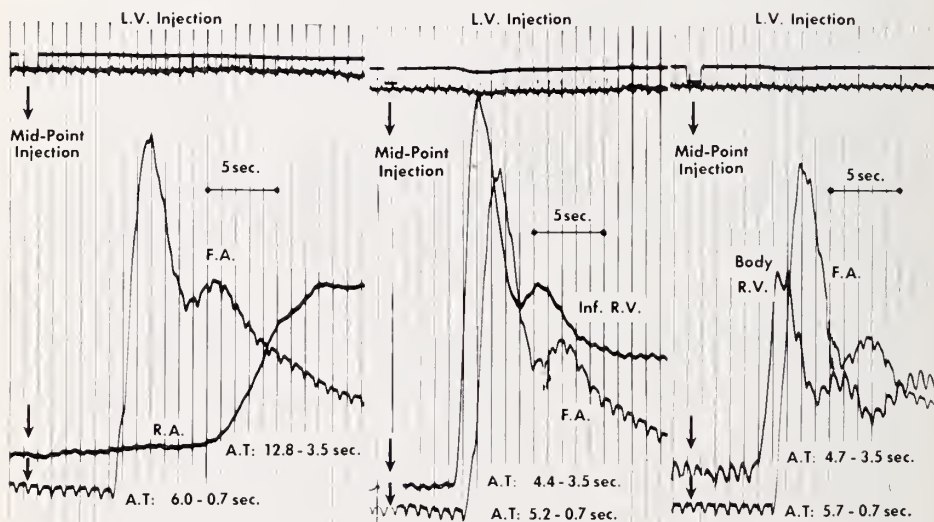


FIG. 21. Acyanotic Tetralogy of Fallot studied with indocyanine green dilution curves after transeptal left heart catheterization, and left ventricular dye injection. An early appearance time is present after right ventricular but not right atrial sampling. The left to right shunt is thus localized to distal to the tricuspid valve.

patent ductus with shunt reversal. Similar curves are obtained employing ascorbate as the indicator (Fig. 14) in another patient with a patent ductus, pulmonary hypertension and shunt reversal. The appearance time is less from the main than from the distal left pulmonary artery.

N.Rud. I.A. Defect

10/8/63

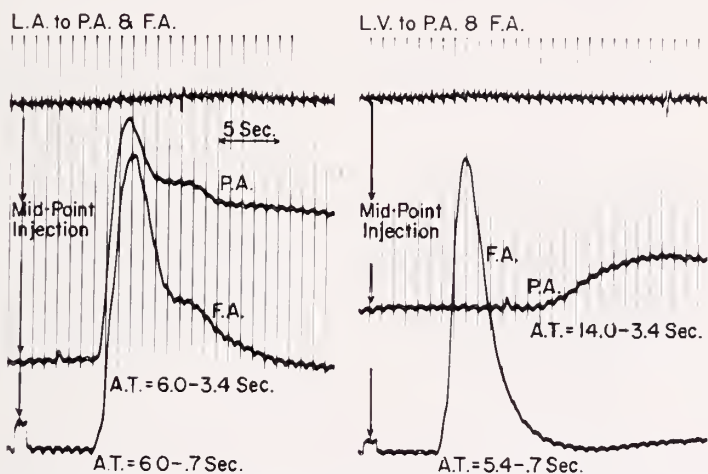


FIG. 22. Ostium secundum atrial defect. The pulmonary and femoral artery indocyanine green dilution curves are abnormal after left atrial but not left ventricular dye injection, thus localizing the left to right shunt to upstream to the mitral valve.

N.Can. I.A. Defect 6-15-61

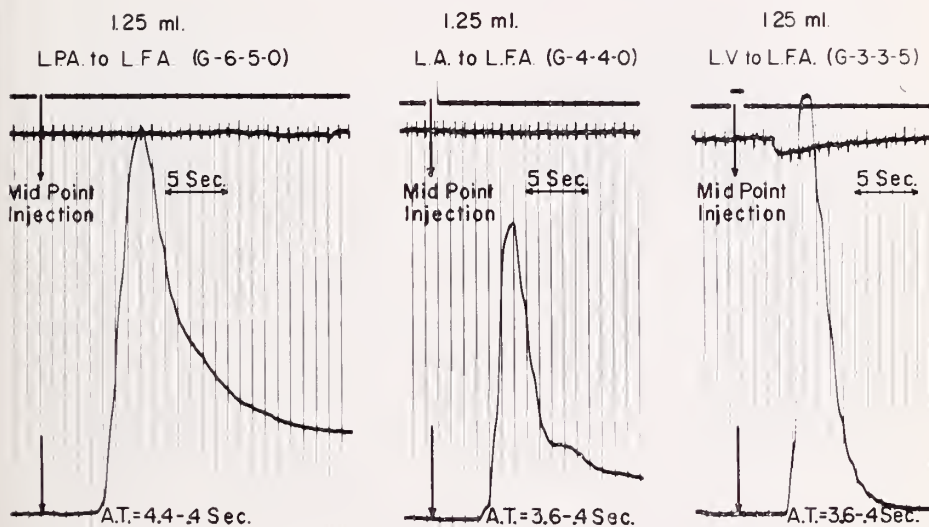
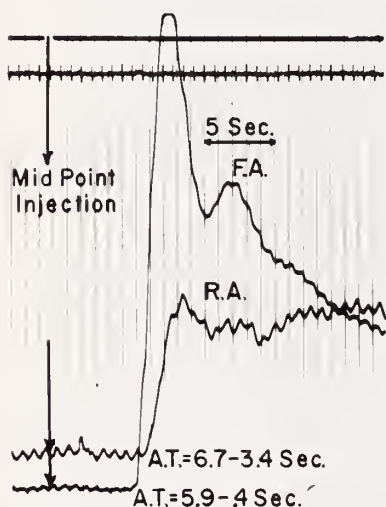


FIG. 23. Ostium secundum atrial defect. The pulmonary artery and left atrial curves are abnormal; that after left ventricular injection is normal. Diagnosis verified at surgery.

The role of indicator dilution curves in the study of patients with varied types of interventricular septal defects will be evaluated next. The patient illustrated in Figure 15 exhibited normal right heart pressures. Pulmonary artery dye injection resulted in an early right ventricular but not an early right atrial appearance time, highly suggestive of a left to right shunt at the ventricular level. Ascorbate dilution curves in another subject with normal right heart pressures and interventricular septal defect are shown in Figure 16. After the spike caused by the ascorbate injection itself, an early appearance time is evident in the right ventricular but not the right atrial curve, confirming a left to

### N. Can. I.A. Defect 6-15-61

RPA to RA (C-8-5-0) and L.F.A. (G-6-6-0)



RPA to IVC (C-8-5-0) and L.F.A. (G-6-6-0)

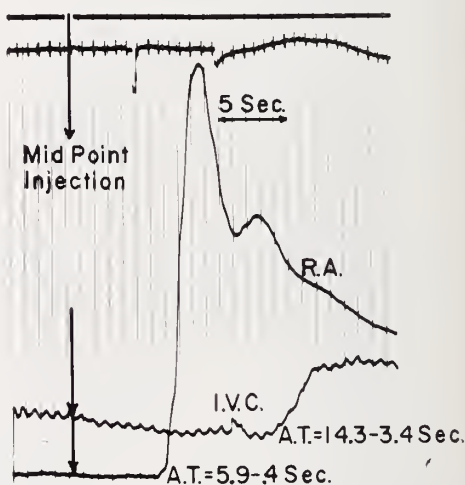
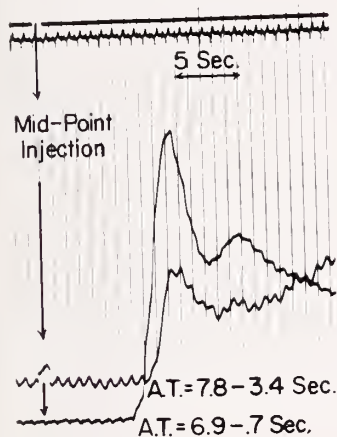


FIG. 24. Same patient as in Fig. 23. Constant pulmonary artery injection site with variable right heart sampling sites. There is an early appearance time after right atrial but not inferior vena cava sampling.

right shunt at the right ventricular level. The localization of a right to left shunt to the ventricular level is demonstrated via Figures 17-18. A double-peaked curve is present after right ventricular and right atrial (Fig. 18) injection, but not after pulmonary artery injection (Fig. 17). In patients with a right to left ventricular shunt with the Tetralogy of Fallot, the shunt may be absent after dye injection in the right ventricular infundibular chamber, and may appear only after indocyanine green injection in the main body of the right ventricle (Fig. 19). Such right to left ventricular shunts are also demonstrable via ascorbate curves (Fig. 20). A typical double-peaked curve is evident. Left ventricular indicator injection (after transeptal left atrial puncture) may aid in the localization of the left to right shunt in a patient with the so-called

F. Cog. I.A. Defect 9/18/61

R.P.A. to Mid RA (C-7-6-0)  
& L.F.A. (G-6-6-0)



R.P.A. to SVC. (C-7-6-0)  
& L.F.A. (G-6-6-0)

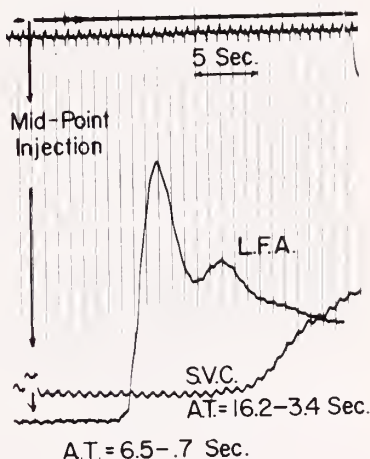
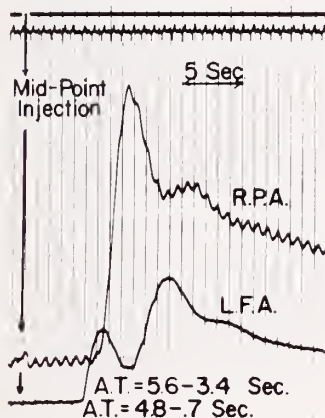


FIG. 25. Ostium primum atrial defect verified at surgery. An early appearance time (after pulmonary artery injection) is present after right atrial but not superior vena cava sampling.

F. Cog. I.A. Defect 9/18/61

L.A. to R.P.A. (C-7-6-0)  
& L.F.A. (G-5-5-0)



L.A. to R.P.A. (C-7-6-0)  
& L.F.A. (G-6-6-0)

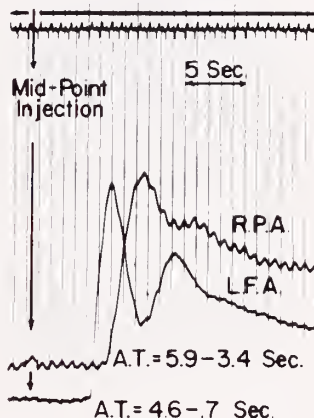


FIG. 26. Same patient as in Fig. 25. A left to right shunt is evident after left atrial injection of ascorbic acid.



## F. Cog. I.A. Defect 9/18/61

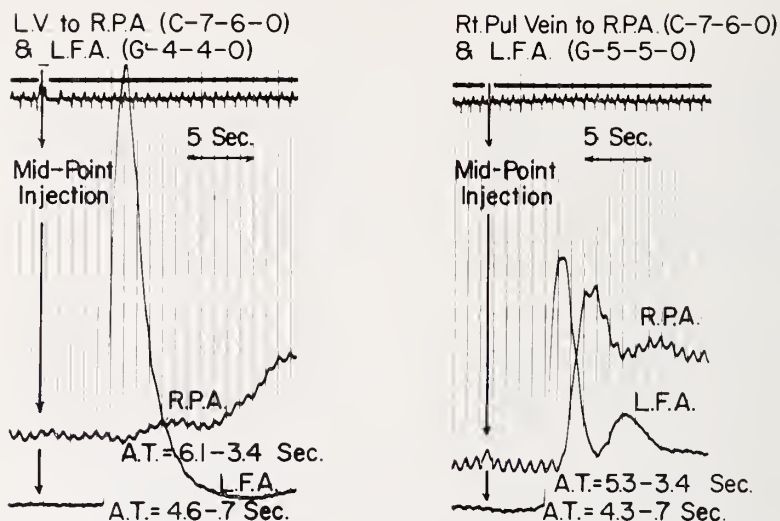


FIG. 27. Same patient as in Fig. 25. An early pulmonary artery appearance time after left ventricular injection is evident (unlike the curves in Fig. 22). A cleft mitral valve with mitral insufficiency was noted at surgery.

## E. Mar. Ostium Secundum Defect 12-12-60

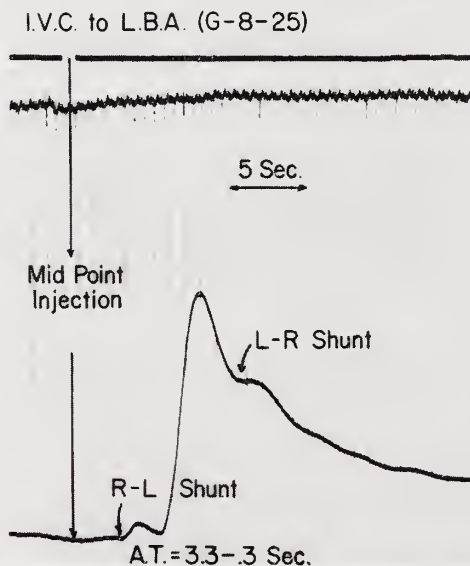


FIG. 28. A right to left shunt with a double-humped brachial artery curve is present in a patient with an ostium secundum defect, after inferior vena cava injection.

acyanotic Tetralogy of Fallot. After left ventricular injection, dye appears early in the right ventricle, but not in the right atrium (Fig. 21).

Our attention will now focus on the role of the indicator dilution curve in the patient with a left to right shunt at the atrial level, in this instance, an ostium secundum defect. The variable injection site, constant sampling site approach is illustrated in Figure 22. Left atrial injection results in an early pulmonary artery appearance time and a deformation of the femoral artery curve downstroke. On the other hand, left ventricular injection is accompanied by a normal peripheral artery appearance time plus a late pulmonary artery appearance time.

R.Ode. Sinus Venosus Type of I.A. Defect  
10/6/60 Rt Anomalous Pulmonary Vein(s)

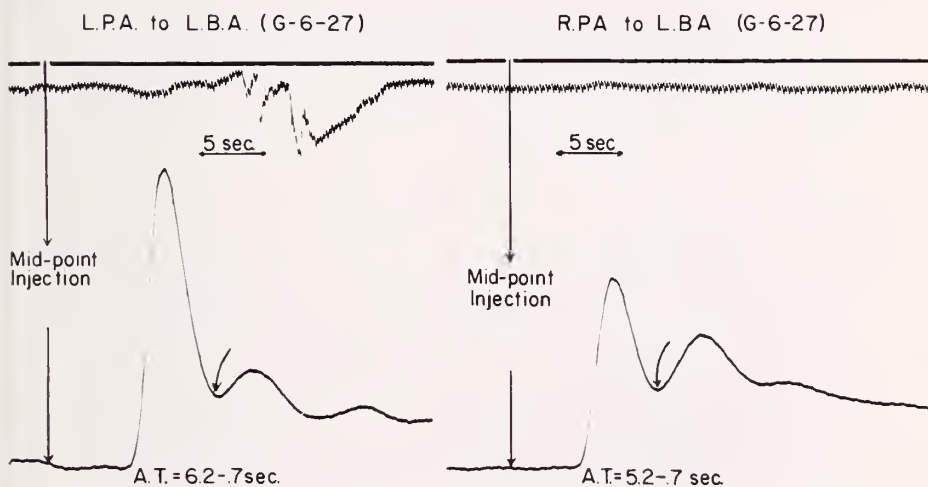


FIG. 29. Right anomalous pulmonary venous connection and drainage with a sinus venosus atrial defect. The left to right shunt is more evident after right than left pulmonary artery injection. See text.

The site of the left to right shunt is thus localized to the atrial level. Comparison of the left pulmonary artery and left atrium as injection sites (Fig. 23) reveals how much more clearly the break on the downstroke of the systemic arterial curve is revealed when the sites of injection and sampling are brought together as much as is possible. The left ventricular injection site in this ostium secundum defect, however, produces a normal systemic arterial dilution curve. One word of caution is in order, however; if one injects in the left ventricle very close to the mitral valve, some of the indocyanine green may leak back to the left atrium and deform the downstroke of the femoral arterial curve even in the absence of mitral regurgitation or an interventricular septal defect. Correspondingly, a left atrial injection near the mitral valve in an ostium secundum defect may force the bolus of dye *en masse* directly into the left ventricle and fail to deform the systemic

arterial curve or produce an early appearance time in the simultaneously sampled pulmonary artery site. Multiple left atrial and ventricular injections are required to avoid these potential pitfalls. Localization of the site of the left to right shunt (ostium secundum defect) may also be performed by the constant injection and variable sampling site method (Fig. 24). After pulmonary artery injection, dye appears early in the right atrium (3.3 sec.), but not in the inferior vena cava (11.0 sec.).

R.Ode. Sinus Venosus Type of I.A. Defect  
10/6/60 Rt. Anomalous Pulmonary Vein(s)

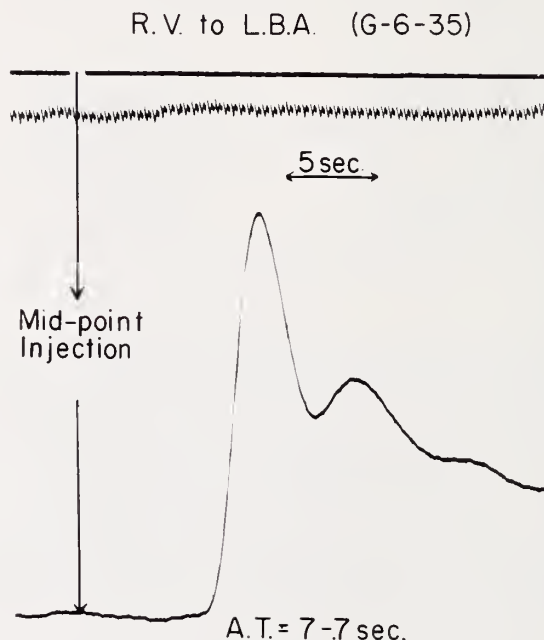


Fig. 30. Same patient as in Fig. 29. There is no right to left shunt after right ventricular injection.

Somewhat different results may be anticipated in an ostium primum defect (Fig. 25-27). Pulmonary artery injection demonstrates an early appearance time in the right atrium, but not superior vena cava (Fig. 25). Left atrial injection (Fig. 26) illustrates an early appearance time in the pulmonary artery plus a marked deformation of the femoral arterial curve. The latter has a double-peaked appearance suggestive of a right to left shunt. However, the first peak is due to dye circulating along a normal pathway; the second peak, although larger than the first (left side of figure) represents the left to right shunted dye. Left ventricular injection (Fig. 27) shows an early pulmonary artery appearance time due either to mitral regurgitation or an additional de-

feet at the ventricular level. A cleft mitral valve with mitral regurgitation was noted at surgery.

Right to left shunts are not infrequently present in patients with ostium secundum interatrial septal defects even in the absence of pulmonary hypertension. These shunts are especially evident after inferior vena cava dye injection (Fig. 28) and rarely seen after superior vena cava injection. There is another variety of interarterial defect which is associated with right pulmonary anomalous venous drainage, usually at the junction of the right atrium and

R.Ode. Sinus Venosus Type of I.A. Defect  
10/6/60 Rt. Anomalous Pulmonary Vein(s)

I.V.C. to L.B.A. (G-6-42) (2" ↓ R.A.)

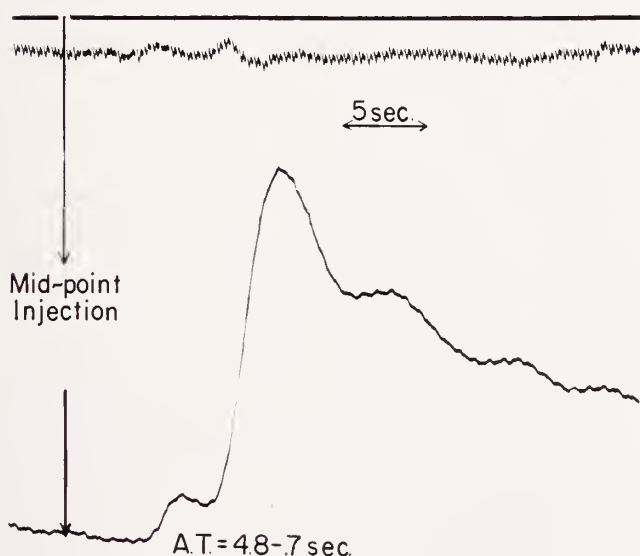


FIG. 31. Same patient as in Fig. 29. A small right to left shunt is evident after inferior vena cava indocyanine green injection.

superior vena cava. This is the so-called sinus venosus defect. The left to right shunt (which even in the ostium secundum defect is preferentially from the right lung) is much greater from the right than from the left lung (Fig. 29). The right ventricular injection site (Fig. 30) fails to reveal a right to left shunt unlike the inferior vena cava injection site (Fig. 31). However, unlike the data in the ostium secundum defect, right atrial (Fig. 32) and especially superior vena cava injection sites (Fig. 33) reveal an obvious right to left shunt even more evident than after inferior vena cava injection. A sinus venosus defect may be anticipated under these circumstances.

Anomalous pulmonary venous connection and drainage may be present with-

out an interatrial septal defect. Such drainage may occur from either the right or the left lung. Left pulmonary anomalous drainage is illustrated in Figure 34. The indicator dilution curves after right pulmonary artery injection are normal; those after left pulmonary artery injection reveal an early right atrial appearance time. The actual site of drainage was into the left innominate vein as evidenced by multiple indicator curves. Right pulmonary anomalous venous drainage without an atrial defect is illustrated in Figures 35–39. Right pulmonary artery injection (Fig. 35) reveals an early right atrial appearance time.

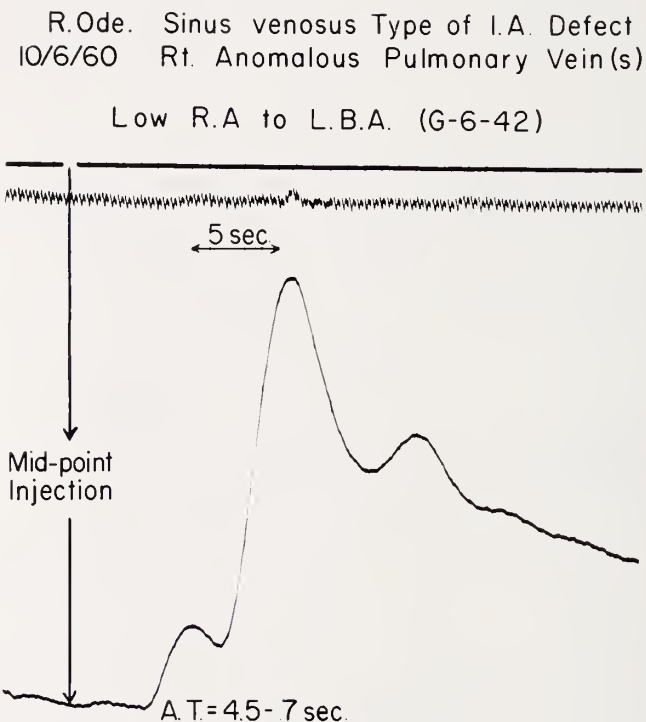


FIG. 32. Same patient as in Fig. 29. A right to left shunt is noted after right atrial injection.

Movement of the second sampling catheter to the inferior vena cava, 4" below the diaphragm, revealed a normally delayed appearance time. At angiography, the right lower lobe pulmonary vein was noted to drain into the inferior vena cava about 1½" below the diaphragm. The chest film (Fig. 35A) shows the anomalous pulmonary vein descending along the right border of the heart to pass through the diaphragm. Left pulmonary artery injection (Figs. 36–37) in the same patient revealed a normal femoral arterial curve and normally delayed right heart appearance times. Ascorbate dilution curves with pulmonary artery injection and sampling (Fig. 38) demonstrate an early appearance time via the right, but not the left, pulmonary artery. Injection of ascorbate acid



R.Ode. Sinus Venosus Type of I.A. Defect  
10/6/60 Rt. Anomalous Pulmonary Vein(s)

S.V.C. to L.B.A. (G-6-42)(1 1/2" ↑ R.A.)

S.V.C. to L.B.A. (G-6-42)(3 1/2" ↑ R.A.)

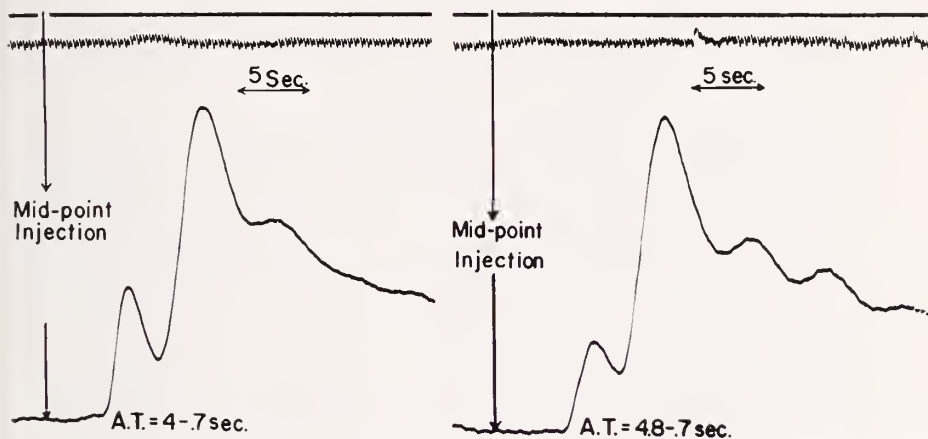


FIG. 33. Same patient as in Fig. 29. The right to left shunt is best noted after superior vena cava injection. See text.

F.Mit. L.Anom. Pul. Vein

7/27/63

R.P.A. to F.A. and R.A.

L.P.A. to F.A. and R.A.

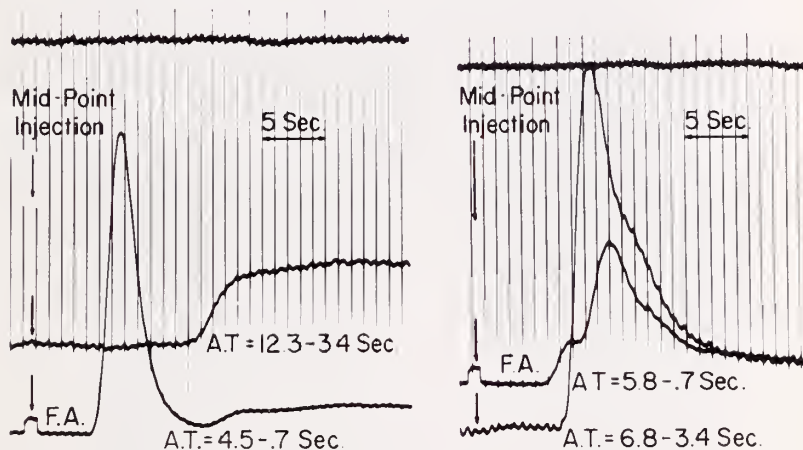


FIG. 34. Left anomalous pulmonary venous connection and drainage to the left innominate vein without an interatrial septal defect, verified by angiography and transeptal left heart catheterization. A left to right shunt is evident after left but not right pulmonary artery injection sites.

T. Mat. 7-6-63

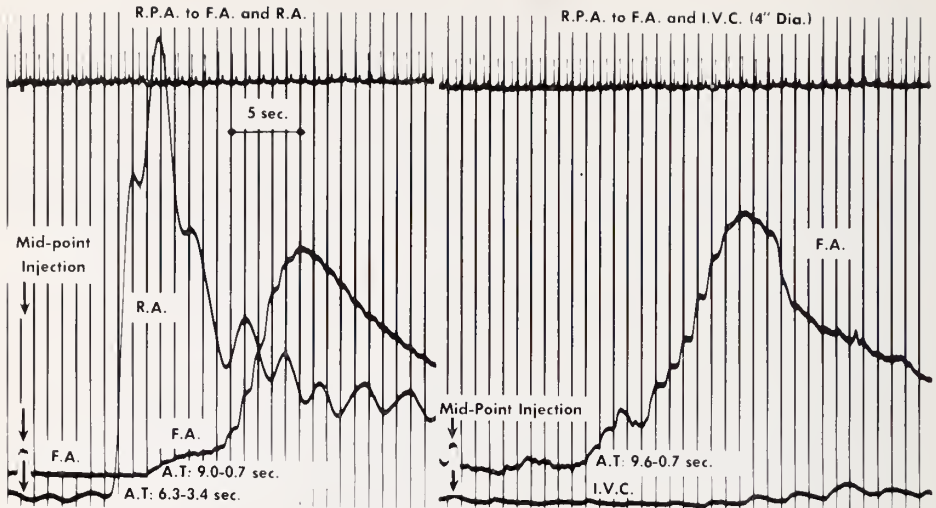


FIG. 35. Right anomalous pulmonary venous connection and drainage verified by angiography. After pulmonary artery injection an early right heart appearance time is evident in the right atrium but not in the inferior vena cava 4'' below the diaphragm.



FIG. 35A. Chest film showing anomalous pulmonary vein descending along right cardiac border.

into either pulmonary artery with systemic arterial sampling (Fig. 39) reveals a normal curve after left pulmonary arterial injection, but a large left to right shunt after right pulmonary artery injection. As mentioned earlier, the first

### T. Mat. Anom. Pul. Vein

7/6/63

L.P.A. to R.A. and F.A.

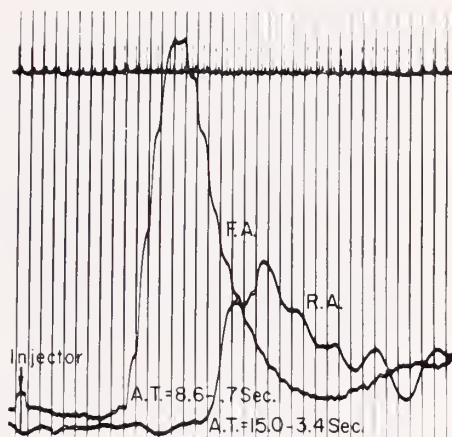


FIG. 36. Same patient as in Fig. 35. Left pulmonary artery injection is associated with normal right atrial and femoral artery indocyanine green curve.

### T. Mat. Anomalous Pul. Vein

10/19/62

L.P.A. to L.F.A. and R.V.

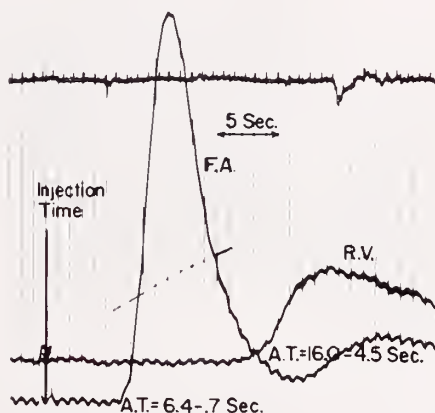


FIG. 37. Same patient as in Fig. 35. Left pulmonary artery dye injection results in normal curves.

peak in the latter curve is caused by the ascorbate following a normal circulatory pathway; the second peak is caused by the large left to right shunt.

These same principles may also be applied to the detection and localization of acquired shunts such as an acquired systemic arterio-venous traumatic

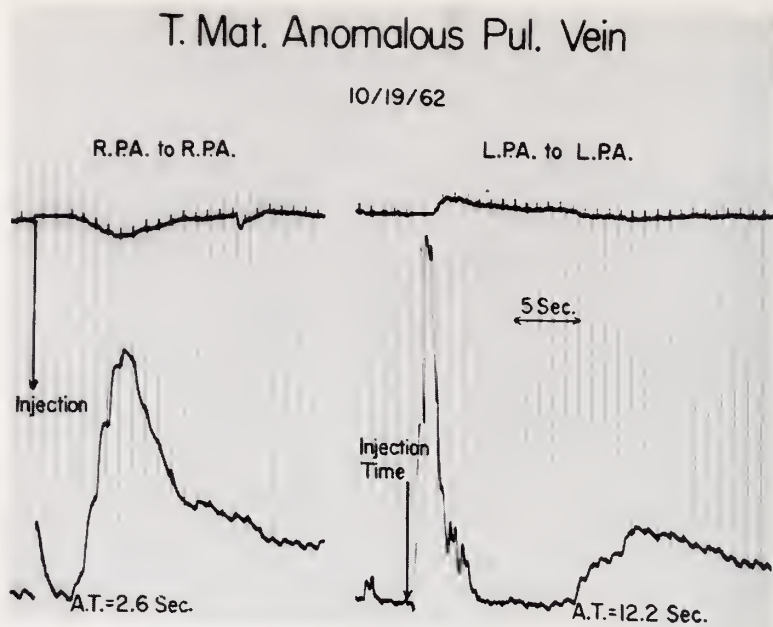


FIG. 38. Same patient as in Fig. 35. Ascorbate right and left pulmonary artery curves reveal an early appearance time and therefore a left to right shunt after right but not left pulmonary artery injection.

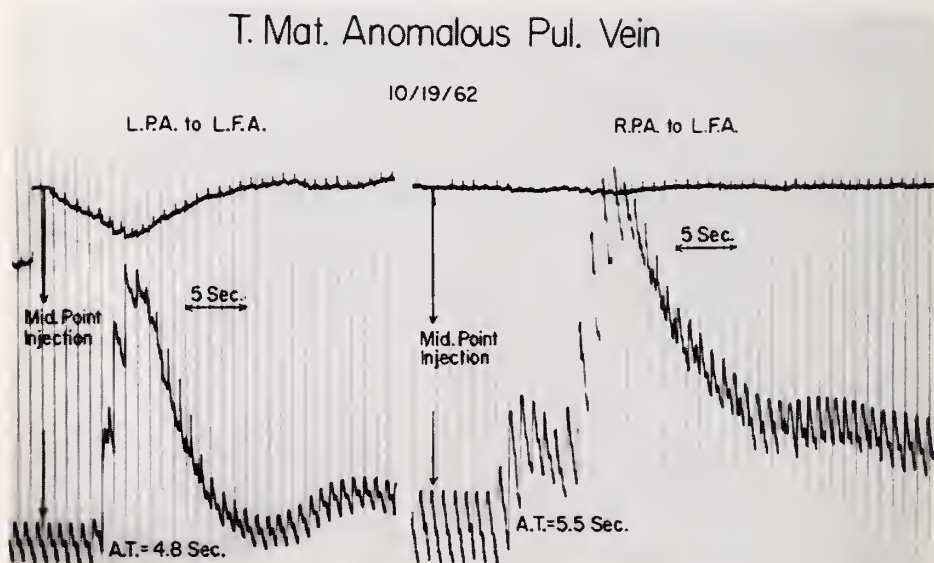


FIG. 39. Ascorbate pulmonary artery injection with systemic arterial sampling reveals left to right shunt only after right pulmonary artery injection.

# J. Pow. Systemic a-v fistula patent

R.P.A. to R.A. (C-6-6-0) and L.F.A. (G-6-6-0) 1.25 ml.

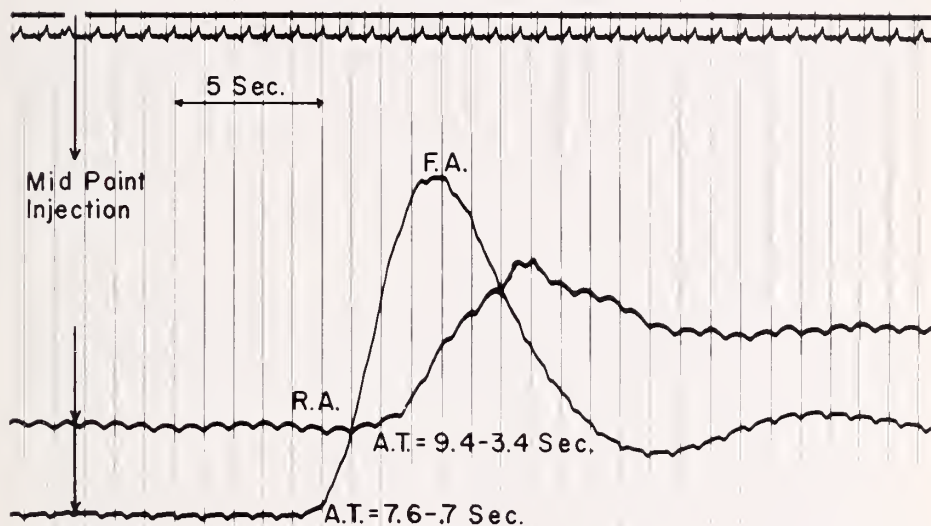


FIG. 40. Traumatic acquired systemic arterio-venous fistula. See text for details.

# J. Pow. Systemic a-v fistula occluded

R.P.A. to R.A. (C-6-6-0) and L.F.A. (G-6-6-0) 1.25 ml.

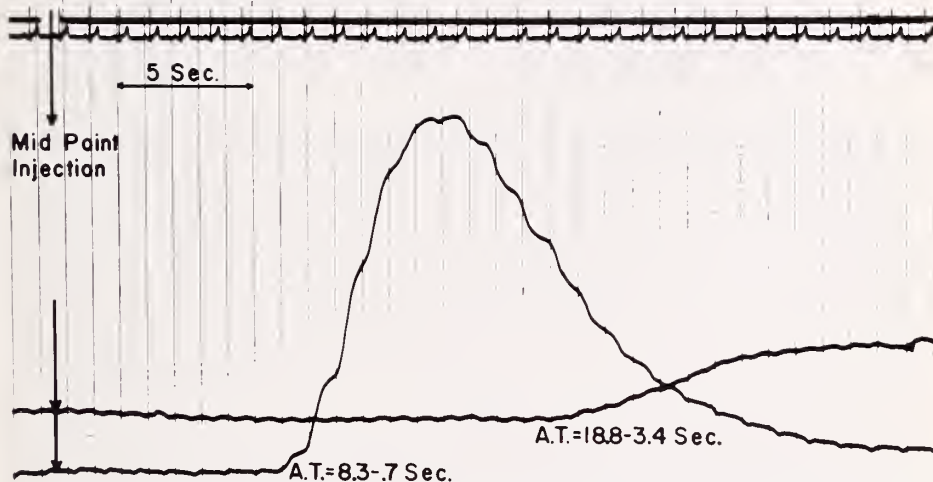


FIG. 41. Same patient as in Fig. 40. Manual compression of the fistula eliminates the left to right shunt and the evidence of the early right atrial dye appearance time.

fistula (Figs. 40-41). The site of the shunt was the left external carotid artery to the left internal jugular vein; the etiology was a knife stab wound. Pulmonary artery injection reveals an early right atrial appearance time with an early re-circulation pattern in the femoral arterial curve. Manual compression of the fistula (Fig. 41) abolished these abnormalities. The curves after surgical correction of the lesion were similar to the occlusion dilution curves.

Valvular regurgitation may also be detected by similar techniques. Left ventricular indocyanine green injection in a patient with mitral regurgitation results in an earlier left atrial than femoral artery appearance time (Fig. 42).

#### MITRAL REGURGITATION

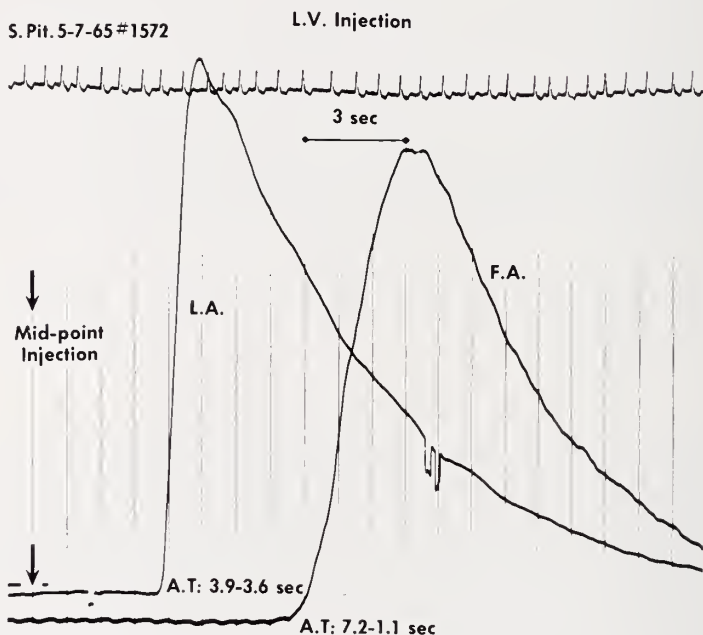


FIG. 42. Mitral regurgitation. Left ventricular indocyanine green injection with left atrial sampling. The left atrial appearance time is virtually immediate.

Similarly, pulmonary artery injection in pulmonary valvular regurgitation (Fig. 43) causes an earlier appearance time in the right ventricular outflow tract than in the brachial artery curve.

The dilution techniques employing indicators that may be concentration calibrated in the patient's blood permit calculation of total cardiac output and segmental blood volumes. Indeed these constituted the earliest applications of the indicator dilution techniques (1, 2). Numerous studies have attested to the value of the indicator dilution approach for the determination of cardiac output and segmental blood volumes and several groups have compared the direct Fick and indicator dilution cardiac output methods in the same subjects (15-19). Right atrial or superior vena cava dye injection combined with sampling



from both the pulmonary and systemic arterial systems has permitted determination of right and left ventricular outputs (20). The reproducibility of the indocyanine green cardiac output technique is at least as good as that of the direct Fick method (21). A recent study by Rahimtoola and Swan (22) has raised a question as to the validity of the indicator dilution cardiac output method in the presence of mitral regurgitation if the indicator is injected upstream to the ascending aorta. A study of over 500 patients in our laboratory with concurrently determined pulmonary and systemic arterial dye dilution curves (23) suggests strongly that the doubts raised by Swan's study are of little concern as long as a valid semi-log extrapolation of the downstroke of the

D. War. Valvular P.S. 4 yrs. post-op.; post-op. pul. insuff. 12-1-60

R.P.A. to R.V. (C-8-30) and L.B.A (G-5-25) ( $\frac{Q}{F} = \frac{27}{27}$  by wedge)

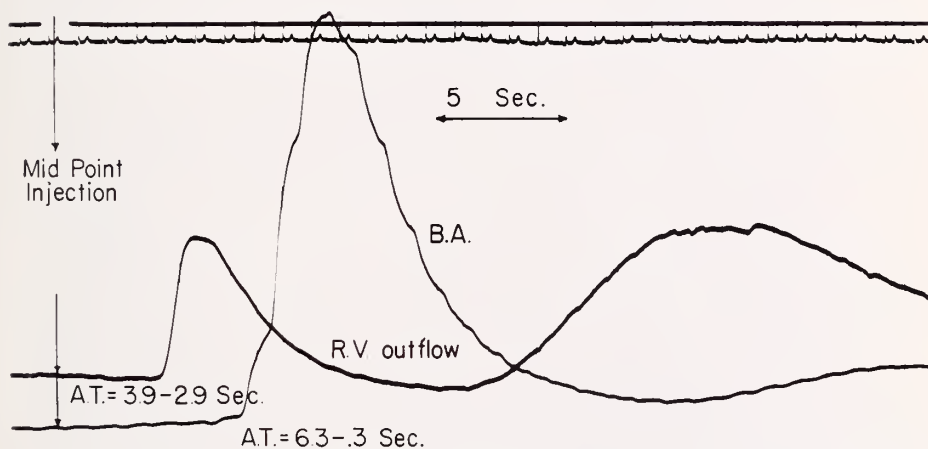


FIG. 43. Pulmonary valvular regurgitation. Pulmonary artery indocyanine green injection with right ventricular sampling. The dye appears early in the right ventricle in the absence of a left to right shunt.

arterial dilution curve is possible. When such an extrapolation may not be done with validity, one may employ the pulmonary arterial curve for calculation of cardiac output if the indicator is injected upstream to the tricuspid valve. Radioactive krypton may also be advantageously utilized for right ventricular output determination in patients with mitral regurgitation (24). The recent development of cardiac output dye dilution computers promises to shorten the time required for these determinations.

#### SUMMARY

Some of the various applications of indicator dilution methods are outlined. Stress has been placed upon the role of indicators in the determination and localization of right to left and left to right cardiac shunts. Other uses of this technique have been mentioned briefly.

## REFERENCES

1. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G.: Simultaneous Determination of Pulmonary and Systemic Circulation Times in Man and of a Figure Related to the Cardiac Output. *Am. J. Physiol.*, 84: 338, 1928.
2. Stewart, G. N.: Researches on the Circulation Time and on the Influences Which Affect It. IV. The Output of the Heart. *Am. J. Physiol.*, 22: 159, 1897.
3. Swan, H. J. C.: Indicator Dilution Methods in the Diagnosis of Congenital Heart Disease. *Prog. Cardiovasc. Dis.* 2: 143, 1959.
4. Wood, E. H., Swan, H. J. C., and Helmholtz, H. F., Jr.: Recording and Basic Patterns of Dilution Curves: Normal and Abnormal. *Proc. Staff Meet. Mayo Clin.*, 32: 464, 1957.
5. Hetzel, P. S., Swan, H. J. C., and Wood, E. H.: The Applications of Indicator Dilution Curves in Cardiac Catheterization. In: *Intravascular Catheterization*, p. 539, ed., Zimmerman, H. A. Springfield: Charles C. Thomas 1959.
6. Wood, E. H., Swan, H. J. C., and Marshall, H. W.: Technic and Diagnostic Applications of Dilution Curves Recorded Simultaneously from the Right Side of the Heart and from the Arterial Circulation. *Proc. Staff. Meet. Mayo Clin.*, 33: 536, 1958.
7. Braunwald, E., and Morrow, A. G.: Newer Diagnostic Techniques in Congenital Heart Disease. *Advances Int. Med.*, 10: 41, 1960.
8. Braunwald, E., Tanenbaum, H. L., and Morrow, A. G.: Localization of Left to Right Cardiac Shunts by Dye Dilution Curves Following Injection into the Left Side of the Heart and into the Aorta. *Am. J. Med.*, 24: 203, 1958.
9. Braunwald, E., Pfaff, W. W., Long, R. T. L., and Morrow, A. G.: A Simplified Indicator Dilution Technique for the Localization of Left to Right Circulatory Shunts. Experimental and Clinical Study of Intravenous Injection with Right Heart Sampling. *Circulation*, 20: 875, 1959.
10. Frommer, P. L., Pfaff, W. W., and Braunwald, E.: The Use of Ascorbate Dilution Curves in Cardiovascular Diagnosis. Applications of a Technique for Direct Intravascular Detection of Indicator. *Circulation*, 24: 1227, 1961.
11. Samet, P., Bernstein, W. H., Kramer, C., and Silverman, L.: Indicator Dilution Curves in Congenital Cardiac Lesions Involving the Ventricles and Great Vessels. *Am. J. Cardiol.*, 10: 83, 1962.
12. Samet, P., Bernstein, W. H., Silverman, L., and Kramer, C.: Indicator Dilution Curves in Atrial Septal Defect. *Brit. Heart J.*, 25: 191, 1963.
13. Samet, P., Bernstein, W. H., Jacobs, W., and Fomon, J.: Indicator Dilution Curves in Systemic Arterio-venous Fistulas. *Am. J. Cardiol.*, 13: 176, 1964.
14. Samet, P., Bernstein, W. H., and Medow, A.: Ascorbic Acid Indicator Dilution Curves. *Southern Med. J.*, 57: 536, 1964.
15. Hamilton, W. F., Riley, R. L., Attyah, A. M., Cournand, A., Fowell, D. M., Himmelstein, A., Noble, R. P., Remington, J. W., Richards, D. W., Jr., Wheeler, N., and Witham, A. C.: Comparison of Fick and Dye Injection Methods of Measuring Cardiac Output in Man. *Am. J. Physiol.*, 153: 309, 1948.
16. Werko, L., Lagerlog, H., Buch, H., Wehle, B., and Holmgren, A.: Comparison of the Fick and Hamilton Methods of the Determination of Cardiac Output in Man. *Scandinav. J. Clin. & Lab. Invest.* 1: 109, 1949.
17. Milnor, W. R., Jose, A. D., and McGaff, C. J.: Pulmonary Vascular Volume, Resistance and Compliance in Man. *Circulation*, 22: 30, 1960.
18. Dock, D. S., Kraus, W. L., McGuire, L. B., Hyland, J. W., Kraus, F. W., and Dexter, L.: The Pulmonary Blood Volume in Man. *J. Clin. Invest.*, 40: 317, 1961.
19. Oakley, C., Glick, G., Luria, M. N., Schreiner, B. F., Jr., and Yu, P. N.: Some Regulatory Mechanisms of the Human Pulmonary Vascular Bed. *Circulation*, 26: 917, 1962.
20. Fritts, H. W., Jr., Harris, P., Chidsey, C. A., III, Clauss, R. H., and Cournand, A.: Validation of a Method for Measuring the Output of the Right Ventricle in Man

by Inscription of Dye-dilution Curves from the Pulmonary Artery. *J. Applied Physiol.*, 11: 362, 1957.

21. Samet, P., and Bernstein, W. H.: Unpublished Data.
22. Rahimtoola, S. H., and Swan, H. J. C.: Calculation of Cardiac Output from Indicator-dilution curves in the Presence of Mitral Regurgitation. *Circulation*, 31: 711, 1965.
23. Samet, P., and Bernstein, W. H.: In press (*Circulation*).
24. Cornell, W. P., Braunwald, E. and Brockenbrough, E. C.: Use of Krypton<sup>85</sup> for the Measurement of Cardiac Output by the Single-injection Indicator-dilution Technique. *Circulation*, 9: 984, 1961.

# Acute Iron Poisoning

## Clinical and Laboratory Observations with Deferoxamine\*

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Acute iron poisoning in children usually occurs from accidental ingestion of medicinal iron and is associated with a high mortality if therapy is not instituted rapidly (1-3). Deferoxamine therapy seems to be highly specific for this acute intoxication and fatal reactions may be expected to decrease with early treatment. This paper presents an example of successful deferoxamine therapy for iron intoxication. Laboratory studies performed add to the understanding of the mechanism of action of deferoxamine.

### MATERIALS AND METHODS

The methods for serum iron (4), unsaturated iron binding capacity (4) and urinary iron (5) have been described previously. Other laboratory tests were performed by standard accepted methods. Deferoxamine† was dissolved in saline for parenteral administration and in water for gastric instillation.

### CASE HISTORY

J. W. (C.H.C.E. #242749), an 18-month-old 27 pound male, was noted to vomit green fluid containing partially dissolved tablets just before noon on February 25, 1965. His mother then discovered that her box of ferrous sulfate pills (coated tablets of 0.2 grams each) was empty, and she was unable to account for 18 to 30 tablets (presumably this represents the amount ingested). Upon advice of her physician she gave her son milk which he promptly vomited. This contained additional remnants of iron tablets. The child was brought to the hospital and on admission (about 3:30 p.m.) was alert, active and in no distress with normal vital signs (B.P. 90/50, pulse 110/min, respirations 28/min). No abnormalities were noted on physical examination. Blood was obtained for laboratory studies (Table I) and intravenous therapy was initiated with a solution containing 1 part M/6 sodium lactate, 2 parts isotonic saline and 3 parts 5% glucose in water. At 4:00 p.m. he suddenly became lethargic and had unequal pupils that did not respond to light. Respiratory

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† Deferoxamine kindly supplied as Desferal-methane-sulfonate by Drs. E. A. Jack and W. F. Westlin of CIBA Pharmaceutical Co., Summit, New Jersey.

distress with gasping respirations was noted. Blood pressure and pulse remained normal. Therapy with deferoxamine was instituted, viz., 1.0 Gm was given intravenously, 1.6 Gm subcutaneously and 5.0 Gm in 40 ml water intragastrically via a nasogastric tube. One half of the intravenous dose was given in a thirty minute period and the remaining 0.5 Gm within the next hour. The gastric contents, aspirated immediately prior to installation of deferoxamine, were slightly blood tinged but otherwise appeared normal. Within thirty minutes after therapy was initiated the child became alert, with normal respirations and eye signs. During the infusion of deferoxamine, blood pressure and pulse remained normal. Later that evening a transient fever of 101° F. occurred, and penicillin therapy was instituted when coarse breath sounds were heard. The

TABLE I  
*Peripheral Blood Studies*

Time	Fe ( $\mu$ g/100 ml)	TIBC ( $\mu$ g/100 ml)	Hgb (gm/ 100 ml)	Hct. (%)	Retics (%)	CO <sub>2</sub> (mEq/l)	Cl (mEq/l)	Na (mEq/l)	K (mEq/l)	BUN (mg/ 100 ml)
2/25/65										
4:00 PM	800		8.3	29		21	101	139	3.8	20
6:15 PM	298									
10:15 PM	102		8.6	29		14	115	151	4.8	19
2/26/65										
3:00 AM	46	516	7.0	27						
9:00 PM	100	565	7.9	27.5	2.1					
3:00 PM	90									
3/1/65			8.4	28	7.8					
3/2/65					4.1					

child improved rapidly, and was discharged on the sixth hospital day when the lesions of chickenpox appeared.

*Laboratory Studies (Table I)*

The child had a microcytic, hypochromic anemia (MCV 68  $\mu$ , MCHC 29%, MCH 19  $\mu$ gm) and the peripheral smear revealed microcytic, hypochromic red cells. Bone marrow aspiration performed twenty-four hours after admission demonstrated a myeloid-erythroid ratio of 1:1, nucleated red cell precursors with ragged cytoplasmic borders, and absence of iron by Prussian blue staining. An absolute reticulocytosis was present on the fifth and sixth hospital days. Blood chemistries showed evidence of increasing sodium and chloride concentration and decreasing carbon dioxide combining power compatible with hypernatremic dehydration and a metabolic acidosis. The initial serum iron concentration which was elevated to 800  $\mu$ g/100 ml, rapidly decreased after deferoxamine therapy. Admission urinalysis was normal except for a trace of protein. Total urinary excretion of iron, for the two day period after therapy, was 1.6 mg. This represents a minimal value because urine collections were incomplete.



*Special Studies of Serum Iron and Iron Binding Capacity (Table II)*

The rapid decrease of serum iron concentration within one hour after institution of therapy posed the question of the adequacy of analytic methods for serum iron in the presence of deferoxamine. In vitro studies clearly demonstrate that deferoxamine will competitively chelate plasma bound iron. Such deferoxamine bound iron is undetectable by the Schade (4) analytic procedure. Upon addition of a strong reducing agent, such as 2 mg  $\text{Na}_2\text{S}_2\text{O}_4$  per ml of plasma (after incubation with the Schade reagents) this iron can be detected. Deferoxamine bound iron in aqueous solution however, is readily detected by the Schade method (4) without addition of any  $\text{Na}_2\text{S}_2\text{O}_4$ .

Deferoxamine in plasma and in aqueous solution behaves, in the chemical analysis, as unsaturated iron binding capacity (UIBC). The UIBC given for

TABLE II

Plasma, Control	Plasma with Df <sup>d</sup>	Plasma with $\text{Na}_2\text{S}_2\text{O}_4$	Plasma with Df <sup>d</sup> and $\text{Na}_2\text{S}_2\text{O}_4$
76/152	40/576 <sup>a</sup>	78/	77/ <sup>a</sup>
85/	36/ <sup>b</sup>	90	95/ <sup>b</sup>
94/185	8/608 <sup>c</sup>		
192/113	13/609 <sup>c</sup>		

Iron (numerators) and unsaturated iron binding capacities (UIBC) (denominators) in  $\mu\text{g}/100$  ml of plasma. There is an apparent decrease in serum iron concentration and an apparent increase in UIBC when deferoxamine is added to plasma. When  $\text{Na}_2\text{S}_2\text{O}_4$  is added to the analytic procedure (see text) the true serum iron is measured. An aqueous solution of 0.05 mg. deferoxamine per ml of water gave a 0/438 result (theoretical 0/425), and an aqueous solution of ferrioxamine a 225/552 result (theoretical 233/>>600).

<sup>a</sup> 0.05 mg Df/ml plasma.

<sup>b</sup> 0.2 mg Df/ml plasma.

<sup>c</sup> 2.0 mg Df/ml plasma.

<sup>d</sup> Df = deferoxamine.

deferoxamine (Table II) represents the upper limit that can be assayed, by this system (600  $\mu\text{g}/100$  ml).

## DISCUSSION

The signs and symptoms of acute iron intoxication shown by this child included vomiting, respiratory distress, ocular changes, metabolic acidosis, and a pathologically elevated serum iron concentration. The respiratory and ocular signs were probably central nervous system in origin, associated with intracellular acidosis and enzyme inhibition (6) by the iron. The hyperchloremia and decreasing carbon dioxide combining power were controlled by fluid therapy and posed no obvious problem.

The child had iron deficiency anemia with microcytic, hypochromic red cells and marrow normoblast abnormalities. The iron deficiency afforded a modicum of protection against iron intoxication, but when challenged by an ingested dose of 1.26 to 2.10 Gm of iron, the "defense" of the preexisting hypoferrremia



was rapidly overwhelmed and toxic symptomatology developed. It is of interest that a reticulocytosis ensued (Table I), a dubious benefit of this intoxication.

Deferoxamine has been used successfully for the treatment of acute iron toxicity (7, 8). Our patient and another reported case (7) showed significant improvement within minutes after intravenous administration of deferoxamine. The explanation for the rapid improvement undoubtedly is related to deferoxamine's high stability constant for iron,  $10^{31}$  (9), and to its rapid *in vivo* distribution. Studies by Keberle (9) suggest that deferoxamine diffuses rapidly into the intracellular as well as the extracellular space. This rapid diffusion permits widespread chelation of ionic iron (ferrous and ferric) (9), resulting in rapid detoxification.

The decrease in serum iron concentration from 800 to 298  $\mu\text{g}/100\text{ ml}$  (Table I) in less than  $1\frac{1}{2}$  hours after beginning deferoxamine therapy is at least partially factitious. The explanation for this is evident from the *in vitro* studies. These experiments (Table II) demonstrate that when deferoxamine is added to plasma, a significant fraction of the serum iron is not detected by the Schade (4) method. Deferoxamine has a higher stability constant for ferric iron than does transferrin (9) and, therefore, can chelate iron that is bound to transferrin. In plasma, an oxidizing system for ferrous cation, the Schade reagents (4) cannot reduce the ferric cation in ferrioxamine to ferrous cation. Ferric iron cannot combine with the Schade (4) chromogen to give the color needed for analysis. A strong reducing agent in adequate concentration, 2 mg.  $\text{Na}_2\text{S}_2\text{O}_4$  per ml of plasma, is needed for this reduction to ensure detection of all iron present in the plasma. In aqueous systems, however, the Schade reagents (4) have sufficient reducing activity to permit detection of the ferrioxamine iron (Table II). Sufficient plasma from the patient was not available to repeat the analysis with the addition of  $\text{Na}_2\text{S}_2\text{O}_4$ . Studies on other patients who were given deferoxamine, however, have confirmed this interpretation (10).

Serum iron determinations by the Ramsey method (11) are also spuriously low if the plasma contains deferoxamine (10), and as with the Schade technique (4) the addition of  $\text{Na}_2\text{S}_2\text{O}_4$  permits valid detection of all iron in the serum.

Observations in this patient suggest that circulating deferoxamine-bound-iron is less toxic than "free" (i.e., non-transferrin bound) iron. They also suggest that the Schade (4) or Ramsey (11) methods of measuring plasma iron may reflect clinically toxic levels better than the "true" total plasma iron level determined after  $\text{Na}_2\text{S}_2\text{O}_4$  treatment of plasma during deferoxamine therapy.

#### SUMMARY

1. A child with acute iron toxicity, due to the ingestion of 1.26 to 2.10 Gm of iron as ferrous sulfate, had a rapid and favorable response to deferoxamine therapy. The rapidity of the response can be explained by deferoxamine's high stability constant for iron, by the rapid *in vivo* distribution of deferoxamine, and by low toxicity of iron which is bound to deferoxamine.

2. A method for the determination of the total iron in serum containing deferoxamine is described.

#### REFERENCES

1. Hoppe, J. O., Marcelli, C. M. A., and Tainter, M. L.: A Review of the Toxicity of Iron Compounds. *Am. J. Med. Sci.*, 230: 558, 1955.
2. Aldrich, R. A.: Acute Iron Toxicity, in: *Iron in Clinical Medicine*, Wallerstein, R. O., and Mettler, S. R., Eds. Berkeley: Univ. of Calif. Press, 1958.
3. Beutler, E., Fairbanks, V. F., and Fahey, J. L.: *Clinical Disorders of Iron Metabolism*. New York: Grune and Stratton, 1963.
4. Schade, A. L., Oyama, J., Reinhart, R. W., and Miller, J. R.: Bound Iron and Unsaturated Iron-binding Capacity of Serum; Rapid and Reliable Quantitative Determination. *Proc. Soc. Exp. Biol. and Med.*, 87: 443, 1954.
5. Gevirtz, N. R., Tendler, D., Lurinsky, G. and Wasserman, L. R.: Clinical Studies of Storage Iron with Desferrioxamine. *New Eng. J. Med.*, 273: 95, 1965.
6. Reissmann, K. R., and Coleman, T. J.: Acute Intestinal Iron Intoxication. II. Metabolic, Respiratory and Circulatory Effects of Absorbed Iron Salts. *Blood*, 10: 46, 1955.
7. Henderson, F., Vietti, T. J., and Brown, E. B.: Desferrioxamine in the Treatment of Acute Toxic Reaction to Ferrous Gluconate. *J.A.M.A.*, 186: 1139, 1963.
8. Santos, A. S., and Pisciotta, A. V.: Acute Iron Intoxication. *Am. J. Dis. Child.*, 107: 424, 1964.
9. Keberle, H.: The Biochemistry of Desferrioxamine and Its Relation to Iron Metabolism. *Ann. New York Acad. Sc.*, 119: 758, 1964.
10. Gevirtz N. R., and Wasserman, L. R.: In press (*J. Peds.*).
11. Ramsey, W. N. M.: The Determination of Iron in Blood Serum or Plasma. *Biochem. J.*, 53: 227, 1953.

# Dupuytren's Contracture Associated with Liver Disease

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The association of Dupuytren's contracture with alcoholism and alcoholic liver cirrhosis was first pointed out by Wolfe, Summerskill and Davidson (1). This association has been widely accepted but there have been few reports in the literature confirming or contraverting this important observation (2). We have therefore studied this phenomenon in a series of patients with liver disease of varying etiology, including cirrhosis of the liver, with the purpose of correlating the incidence of Dupuytren's contracture with impaired liver function.

Ninety patients (48 male and 42 female) with liver disease were studied over a 2 year period. Diagnosis was established by appropriate clinical picture, liver function tests and biopsy. There were 62 subjects with cirrhosis of the liver, 10 with carcinoma of the liver (9 metastatic and 1 primary), 7 with hepatitis (5 infectious and 2 homologous serum), 7 with obstructive jaundice due to common duct stone and cholelithiasis, 2 with congestive splenomegaly (Banti's syndrome), 1 with cardiac cirrhosis and 1 with fatty liver. Ages ranged from 35 to 81 in the female group and from 17 to 85 in the males.

The degree of contracture was classified as designated by Moorhead (2) as follows:

- 1st degree: Nodulation with or without dimpling of the skin.
- 2nd degree: Bands or rugae with or without nodulation.
- 3rd degree: Contracture of the fingers with or without bands.
- 4th degree: Combination of 1, 2 and 3.

Of the 62 cases of liver cirrhosis (Laennec type), there were 36 males and 20 females with moderate to heavy alcohol consumption and 6 with only occasional alcohol consumption. Thirty-four or 54.8 per cent of this group showed Dupuytren's contracture. In the 28 patients with non-cirrhotic liver disease, 10 or 35.7 per cent had evidence of Dupuytren's contracture (Table I). As will be seen in this table, the incidence of Dupuytren's contracture is almost as common as the incidence of spider angiomas and approximately as high as the incidence of palmar erythema.

Liver function tests were performed in 49 of the 62 cases in whom the clinical diagnosis of alcoholic cirrhosis was made and in the remaining 28 cases with liver disease of other etiology. The tests performed were those in general use in our hospital, including serum bilirubin, serum alkaline phosphatase, thymol turbidity, cephalin flocculation, total protein and A/G ratio, serum cholesterol and cholesterol ester partition, prothrombin time, serum glutamine oxaloacetic transaminase, serum glutamine pyruvic transaminase, liver biopsy and, often,

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B.S.P. excretion. An attempt was made to correlate the presence or absence of contracture with the chemical findings suggestive of impaired liver function.

Six of our 8 cases of cirrhosis with liver function tests indicating severe impairment showed Dupuytren's contracture. Twenty of our 27 cases of cirrhosis with tests indicating moderate impairment of liver function demonstrated Dupuytren's contracture. Of 14 cases with no significant disturbance of liver function, as measured by the tests, 8 showed contracture.

In the remaining 28 cases of liver disease, Dupuytren's contracture was found in only 10 cases. The diagnosis and results are summarized in Table II.

In some of our patients, in spite of heavy alcoholic intake, clinical findings of Laennec's cirrhosis and positive contracture, liver function tests were within normal limits. This supports the opinion of Wolfe *et al.* that prolonged alcoholism may cause Dupuytren's contracture even though liver function was apparently unimpaired.

TABLE I

Type of Liver Disease	No. of Cases	Positive Dupuytren's Contracture	Spider Angiomata	Palmar Erythema
Alcoholic cirrhosis . . . . .	62	34 (54.8%)	40 (64.1%)	35 (56.4%)
Cardiac cirrhosis . . . . .	1	1 (100%) ?	none	1 (100%) ?
Carcinoma of the liver . . . . .	10			
Primary . . . . .	1	5 (50%)	3 (30%)	4 (40%)
Secondary . . . . .	9			
Obstructive jaundice . . . . .	7	2 (28.5%)	1 (14.9%)	1 (14.9%)
Fatty liver . . . . .	1	none	none	none
Banti's syndrome . . . . .	2	1 (50%)	1 (50%)	1 (50%)
Hepatitis . . . . .	7			
Infectious . . . . .	5	1 (14.3%)	1 (14.3%)	1 (14.3%)
Homologous serum . . . . .	2			

An attempt was made to correlate the severity of the contracture and the presumed degree of impairment of liver function as evidenced by abnormal liver function tests. Of 11 cases with severe impairment of liver function on this basis 7 had Dupuytren's contracture; of 40 patients with moderate impairment 24 showed contracture; and of 26 patients with normal liver function tests (but other evidence adequate for the diagnosis) 13 had palmar contracture.

In the 28 cases of liver disease other than alcoholic cirrhosis, liver function tests indicated severe impairment in 3, moderate impairment in 13 and essentially normal function in 12. In this group as a whole Dupuytren's contracture was positive in 10 cases and negative in 18.

Of the 3 patients in this group whose liver function tests indicated severe impairment, one patient with hepatitis showed Dupuytren's contracture and two, one with hepatitis and the other diagnosed as obstructive jaundice did not develop the phenomenon. Of the 13 patients classified as showing moderate alteration in liver function tests, Dupuytren's contracture appeared in 4 and

was absent in 9. The positive cases were 1 of carcinoma of the liver, 2 of obstructive jaundice due to stone and 1 of Banti's syndrome. The group of 9 patients with moderate impairment of liver function and no Dupuytren's contracture included 2 of carcinoma of the liver, 1 of obstructive jaundice, 1 of Banti's syndrome and 5 of hepatitis. Of the 12 patients showing normal liver function tests, including 7 of carcinoma of the liver, 1 of fatty liver, 3 of obstructive jaundice due to stone and 1 of cardiac cirrhosis, there were 5 instances

TABLE II

Type of Liver Disease	No. of Cases	Liver Function Tests		Dupuytren's Contracture	
				Positive	Negative
Alcoholic cirrhosis	49	Severe impairment	8	6	2
		Moderate impairment	27	20	7
		Normal	14	8	6
Carcinoma of the liver	10	Severe impairment	0	0	0
		Moderate impairment	3	1	2
		Normal	7	4	3
Fatty liver	1	Severe impairment	0	0	0
		Moderate impairment	0	0	0
		Normal	1	0	1
Obstructive jaundice	7	Severe impairment	1	0	1
		Moderate impairment	3	2	1
		Normal	3	0	3
Banti's syndrome	2	Severe impairment	0	0	0
		Moderate impairment	2	1	1
		Normal	0	0	0
Cardiac cirrhosis	1	Severe impairment	0	0	0
		Moderate impairment	0	0	0
		Normal	1	1	0
Hepatitis	7	Severe impairment	2	1	1
		Moderate impairment	5	0	5
		Normal	0	0	0

of Dupuytren's contracture and 7 patients who did not show the phenomenon. Dupuytren's was positive in 4 of 7 cases of carcinoma of the liver (all secondary carcinoma), negative in 1 case of fatty liver, negative in 3 cases of obstructive jaundice due to stone and positive in 1 case of severe cardiac cirrhosis.

## COMMENT AND SUMMARY

The presence of Dupuytren's contracture was studied in 90 patients with liver disease of varying etiology. It was found to be present in 44 of the total group. Of 62 cases of alcoholic cirrhosis, 34 were positive for Dupuytren's con-

tracture, and in a group of 28 cases of non-cirrhotic liver disease 10 were positive.

Our findings of 34 instances of Dupuytren's contracture among 62 patients with alcoholic cirrhosis of the liver is in agreement with the results of Wolfe *et al.* (1). An incidence of 10 positive results in 28 cases of non-cirrhotic liver disease is of significance.

No correlation was found between the severity of impairment of liver function and the presence of Dupuytren's contracture in our series (2).

#### REFERENCES

1. Wolfe, Stanley J., Summerskill, William H. J., and Davidson, Charles S.: Thickening and Contracture of the Palmar Fascia (Dupuytren's Contracture). *New England J. Med.*, 255: 559, 1956.
2. Moorhead, John J.: Dupuytren's Contracture: Review of the Disputed Etiology, 1831-1956. *New York State J. Med.*, 56: 3686, 1956.



# Mental Disorders in Acute Encephalitis

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"Mental" changes in patients with diffuse disease of the brain have long been noted. It was particularly marked during observations made of patients with the epidemic encephalitis of von Economo (1-5). Less frequently has this correlation been made during sporadic cases of presumed inflammatory disease of the brain (6-9).

It is the aim of this report to describe some of the behavioral disturbances which may appear in acute inflammatory disease of the brain—phenomena which bear close resemblance to symptoms attributed to certain psychiatric conditions. The resemblance may be so great as to cause initial diagnostic difficulties.

Diagnostic difficulties may indeed occur in the evaluation of patients with depression in the presence of tumors of the brain (10). A recent report would tend to minimize the incidence of schizophrenic-like phenomena in patients with brain tumors (11). In that study it was felt that social and emotional disturbances occur only secondarily in organic brain disease and delusional ideas when they appear, do so only in a "setting of unmistakably advanced neurological findings." This does not appear to be valid for the patients with inflammatory disease of the brain here presented.

These cases were chosen from among the admissions to the Neurology Service of The Mount Sinai Hospital and all but two were personally seen by at least one of the authors. They were sporadic in occurrence. There were one each in 1949, 1956, 1961; three in 1962; two in 1963, and two in 1964. The onset was during the winter in five, spring in one, summer in one, and autumn in three. Nine were females, with ages ranging from seventeen to forty-seven but mainly in the second and third decades. There was one male age 20.

In these 10 cases, involvement of the brain was demonstrated by abnormalities of the spinal fluid, electroencephalogram or definite neurological findings such as seizures, aphasia and extensor plantar signs. Inflammatory disease was presumed because of the clinical course and in most because of increased numbers of leukocytes in the spinal fluid. However, in no case was an etiologic agent or rising titer of antibodies to the available viral antigens demonstrated. Neoplastic mass lesions were ruled out by the clinical course and by appropriate neuroradiologic procedures. Other causes of diffuse brain dysfunction such as toxic metabolic disturbances or various presumably primary demyelinating diseases, such as multiple sclerosis, although not eliminated with certainty, are far less likely in view of the clinical and laboratory findings.

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## CASE REPORTS

*Case 1.* The patient was a 29 year old woman with history of marital difficulties for which she received psychotherapy. She had been concerned with renouncing her religion prior to her marriage. She had also been interested in extrasensory perception. Several weeks after a non-specific rhinitis she felt that everything "tasted like celery." She then complained of paresthesiae in all four extremities and of sounds seeming more distant than they really were. There was a questionable drift of the left arm. Soon afterwards she became withdrawn and then very agitated. She would shout that God was telling her that "everything was all right" and voices told her that she was a "pure virgin." She could hear conversations taking place at distant tables in a restaurant. Colors were more vivid and walls seemed to be closing in on her. She said she felt like a "Picasso [sic] painting of a woman all in cubes walking downstairs."

It was felt that she was "schizophrenic" and she was admitted to a psychiatric hospital. There she was hallucinating and described as "cataleptic." Electroencephalogram showed bilateral slow activity (as slow as 1 cps) with right temporal accentuation. Spinal fluid contained up to 13 leukocytes per cubic millimeter with normal protein and sugar. After several weeks, she was transferred to The Mount Sinai Hospital where she appeared alert but did not respond to verbal commands or painful stimuli. She showed "waxy flexibility." Fever, coma, seizures and dyskinesias followed before eventual recovery and discharge seven weeks after hospitalization. She received four electro-convulsive treatments midway in her hospital stay. On follow-up she appears well with electroencephalogram returned to normal.

*Case 2.* The patient was a 17 year old girl with history of poor school work with sexual promiscuity. She threatened to have a nervous breakdown if her boyfriend left her. Shortly after, she had a generalized headache and fever up to 102. This cleared but her behavior became more abnormal in the sexual area. She suggested performing sexually perverted acts with her boyfriend and her uncle. She masturbated openly. Her speech became "drawling" and there was some clumsiness of her gait. She ate with her fingers. She was incontinent and unconcerned about it. An initial spinal tap was said to be normal and she was given an electro-convulsive treatment on the basis of the diagnosis of schizophrenia.

She became sleepy and was then hospitalized at The Mount Sinai Hospital. On the admission examination she was unco-operative. She grimaced and masturbated. Despite the presence of an inconstant left Babinski it was felt that her behavior could be due to "schizophrenia." Intravenous sodium amytal did not make her more communicative. Spinal fluid showed 96 leukocytes per cubic millimeter, 95% lymphocytes and protein 34 mg%. Electroencephalogram was obscured by artifact. Neurologic signs including convulsions, dyskinesias and oculogyric crises developed. Temperature rose as high as 107 before gradually diminishing. There was slow improvement in her behavior but she continued to show episodic rage and used obscene language. She was discharged

after three months requiring later admission to a state mental hospital before being discharged as asymptomatic.

*Case 3.* The patient was a 47 year old woman writer with a long history of intermittent behavioral disturbances. She received a course of electro-convulsive therapy at age 30 because of agitated and phobic behavior. She remained afraid of going outside alone and frightened of elevators. She was able to work as a writer despite this.

Several days following a fever with rhinitis and vomiting, she began to hear voices. She would also compulsively insist on finding out what the middle initial in Nelson A. Rockefeller stood for. The next day she had a grand mal seizure. After this she did not speak and was described as having a "wild stare." The physician by whom she was examined diagnosed her difficulty as psychiatric. However later examination on admission to The Mount Sinai Hospital revealed a severe language disturbance with jargon. She did not respond to painful stimuli or to a burning match brought close to her open eyes. Temperatures were spiking, rising to 104.6. There were 270 lymphocytes per cu mm of spinal fluid, all lymphocytes. Electroencephalogram showed bilateral cerebral dysfunction with slowing accentuated in the left anterior temporal region. Pneumoencephalogram was normal. During recovery the language disturbance decreased but remained severe. Repeat electroencephalogram was normal but she required continued hospitalization. She felt that she was in a dream. She maintained that time was standing still, would not look at a clock and turned them all face down. With phenothiazines the phobias diminished but a mild aphasia remains.

*Case 4.* The patient, a 27 year old divorcee, was reportedly under great stress in a new job beyond her abilities. She developed a sense of malaise and diarrhea. She then was unable to sleep and lost her appetite. Her memory was gone and she was uninterested in life. She heard music that others could not hear. On admission she was immobile. Described as showing a "flattened affect with ludic overtones," she had occasional episodes of screaming and shouting. Spinal tap showed 62 lymphocytes, 5 polymorphs with protein of 51 mg%, EEG was normal. She reported seeing insects and other animals crawling on her bed. She referred frequently to wishing that she was dead and that someone would kill her. On one occasion she attempted to strangle herself and her nurse with a bell cord. She required heavy sedation for control. The temperature was at first normal but within the first week became elevated, rising as high as 106° F. There was gradual improvement and was discharged as asymptomatic ten weeks after onset.

*Case 5.* The patient was a 17 year old school girl who was described as quiet and withdrawn. She had a non-specific febrile illness lasting a day. At this same time she began to have increasingly severe arguments with her parents about discipline. Several weeks later she had several grand mal seizures. Following

hospitalization spinal fluid showed no cells but protein of 70 mg%. Electroencephalogram showed marked slowing at the right anterior temporal region. She was agitated and violent. She was depressed with crying spells. She threatened to kill her parents and siblings as well as herself. She heard voices outside the window but could not understand what they said. She was admitted to The Mount Sinai Hospital at this time. It was felt that the behavioral disturbances with almost schizophrenic like behavior, were, in view of the history of seizures, due to presumed disease of the nervous system. Violent behavior persisted. There were persistent delusions that she was to have an operation on her head as well as a hysterectomy. Fever up to 102 occurred during the first two weeks in the hospital. The electroencephalogram had a decreased amount of alpha on the right and a large amount of irregular and at times continuous slow activity (as slow as 1.25 cps) bilaterally right more than left. A right carotid arteriogram and pneumoencephalogram were normal. She was given a course of eighteen electro-convulsive treatments. There was continued improvement and was discharged asymptomatic 3 months after the onset.

*Case 6.* The patient was a 25 year old married woman who had sexual difficulties and was fearful of becoming pregnant. She had several grand mal seizures. Several days later she was uncommunicative although she appeared alert. She made grunting sounds. She did not react to a burning match brought close to her eyes. She was seen by a psychiatric consultant who described her as catatonic either due to neurologic disease or to a post partum psychosis. Shortly after admission intravenous sodium amytal caused no change. Later in her course it elicited more speech but the content remained the same. She would hold her hands in the air with the fingers spread for long periods. She would bang her head and bite at her fingers. She would cry out "poison me, poison me." She refused to permit the nurses to clean her genitalia repeatedly saying "I'm pregnant" and spoke of being seduced at a party. Spinal fluid showed up to 180 leukocytes per cu mm, at first predominately polymorphonuclear but later mainly lymphocytes. Electroencephalogram was abnormal indicating left and later bilateral cerebral dysfunction most pronounced anteriorly with some activity as slow as 1.25 cps. Fever rose to 103. A course of electro-convulsive therapy was suggested but she improved before it was instituted. She was discharged asymptomatic two months after onset. She has continued to have grand mal seizures controlled by anticonvulsants.

*Case 7.* The patient was a 20 year old college student who had been an outgoing, friendly boy prior to the illness, complained of unusual difficulty with courses during summer school. He received a low grade at the end of the term and afterwards was noted to be depressed and withdrawn. Shortly thereafter he experienced occipital headaches, drowsiness, malaise and fever lasting two days. He later showed photophobia and lethargy. Several days later he began to confabulate about a trip with his parents. On admission he was considered to show schizoid behavior evidenced by lack of affect and by not looking at the



examiner. He would put his head under the bedsheets when spoken to. He was disoriented as to time. Somnolence, memory disturbance, and disorientation for time gradually increased, while calculation and obedience to complex commands remained intact for a longer period. He would drink a great deal of water and was incontinent. Temperature spikes to 104° F occurred. Seizures followed and he was comatose for a number of days. Later he became more alert, but fell asleep readily at any time. There would be long latent periods between being asked a simple question and his response. Spinal fluid on admission to the hospital showed ten leukocytes but later in his course this increased to 216 leukocytes per cubic millimeter (mainly lymphocytes). Pneumoencephalography revealed generalized ventricular enlargement. Bilateral spasticity, occasional grand mal seizures, and evidence of cerebral, midbrain, and hypothalamic disturbance remain almost three years after the onset.

*Case 8.* The patient was a 21 year old woman. She was the youngest of a large family and had been recently married. There were sexual difficulties and concern over pregnancy. She had wept when her husband entered the army four months prior to her admission. Two weeks prior to admission she complained of abdominal cramps and succeeded in having her husband returned on compassionate leave. She cried when he was to leave fearing that he would be killed in a plane crash on his return to his base. The next day she complained of "feeling funny all over" and was unresponsive for several minutes. Several days later she had a generalized convulsion beginning on her right side. Over the next few days she was able to carry on about her house but seemed abnormally euphoric. She made errors in a card game and stated that she did not understand people's speech and could not hear herself. She then began to shout obscenities and throw objects. On admission to another hospital her temperature was 102 and she had stopped speaking and eating. A course of electro-convulsive therapy was planned on the basis of a diagnosis of schizophrenia but with the occurrence of another spontaneous seizure she was transferred to the neurologic service at The Mount Sinai Hospital. At that time she did not speak although her eyes were open. She thrashed about during the examination. There were no focal neurologic signs. There was almost continual grimacing, screaming, sobbing, continuous movements of the head and lips. Thrusting pelvic movements occurred with masturbation. Spinal fluid on admission showed 37 lymphocytes per cubic millimeter, mainly lymphocytes. Protein and sugar were normal. Electroencephalogram was diffusely abnormal consisting of 1-4 cps activity. As she improved she would tend to speak in long series of rhymes "joy, joy joy, soy, soy, soy, foy, foy, foy." She was actively hallucinating talking to her husband and nephews. She gradually improved. Fever as high as 104° F returned to normal. She was discharged asymptomatic following two months of hospitalization. An intravenous amytal test was normal just prior to her discharge as was a pneumoencephalogram.

*Case 9.* The patient was a 16 year old school girl who was described as shy and

TABLE 1

No.	Age	Sex	Mode of Onset	Mental Signs	Neurologic Signs	Laboratory		Course
						EEG	CSF	
1	29	F	Non-specific rhinitis. Abnormal sensations: taste, somatosensory, auditory. Followed by withdrawal, agitation, hallucinations, delusions.	Seclusive, visual and auditory hallucinations catatonia, waxy flexibility, unresponsive to painful stimuli, uncommunicative. Religious content to delusions.	Dyskinesias. ?Seizures. Semicoma. Temp. up to 104.8.	Abnormal bilateral slow with R fronto-temporal accentua.	13 WBC. Protein and sugar normal.	About 3 months.
2	17	F	Headache and fever (102) followed by loss of sexual inhibitions and manners. Gait difficulty, clumsiness, and incontinence.	Resistive, uncommunicative, emotional lability. Masturbation. Obscene language.	Left and later right Babinski, dyskinesias, oculogyric crises, seizures. Temp. up to 107.2.	Technically unsatisfactory.	69 WBC. 95% lym.	Acute: 3 months. Chronic: years.
3	47	F	Fever (103) with URI and vomiting, followed 2 days later by auditory hallucinations, compulsive behavior and 1 day later by GM seizure.	Accentuation of phobias, agitation unresponsive to painful stimuli.	Aphasia, seizures, mild right facial paresis. Temp. up to 104.6.	Abnorm. bilat. with left temp. foci.	Up to 353 WBC, all lym. Protein 107 mg%. Sugar normal.	Acute: 6 weeks. Chronic: persistent dysphasia and phobias.
4	27	F	Malaise, diarrhea, insomnia, agitation, auditory hallucinations, immobility.	Agitation, visual and auditory hallucinations echolalia, homicidal and suicidal thoughts and delusions of death.	Episodes of staring, chewing tongue and unresponsive-ness. Disorientation. Temp. up to 106.	Normal	Up to 67 WBC, 90% lymphs.	10 weeks.
5	17	F	Non-specific febrile illness, increasingly a disciplinary problem. Then seizures 5 days later.	Agitated, auditory hallucinations, depression, violent behavior, homicidal, suicidal.	Seizures, temp. up to 102.	Abnormal bilateral accentuated right posterior.	Protein to 70 mg. No cells.	3 months.



6	25	F	Seizures.	Uncommunicative, incomprehension, to unresponsive to painful stimuli, agitated, injurious to self and others, catatonic, waxy flexibility, posturing, delusions of pregnancy.	Seizures, dyskinesias. Temp. up to 103.	Abnormal left fronto temporal.	Up to 180 WBC, at first 65% polys, later 95% lymphs; protein 95; sugar normal.	2 months.
7	20	M	Difficulty in courses for 3 months fever 101, headaches confabulation.	Episodic disorientation, confabulation, withdrawal, somnolent, memory loss, dissociated affect.	Grand mal seizures, semicoma, increased tone, decerebrate posture, temp. up to 103.	Abnormal diffuse.	Up to 216 WBC, 90% lym., protein 73 mg%, sugar normal.	Seizures persist 2 years.
8	21	F	Period of depression 4 months before hospitalization; abdominal cramps 2 weeks before and depression, fear of husband's death, euphoria, obscene language, throwing objects.	Depression, euphoria, obscene, destructive, mute echolalia, distractible, masturbation, delusions about sex and family.	Paresthesias seizures, dysconjugate eye movements, dyskinesias. Temp. up to 102.	Abnormal diffuse.	37 WBC, 78% lym., protein and sugar normal.	2 months.
9	16	F	Fever (101) and sore throat 2 weeks before, headaches, insomnia, and delusions 2 days before admission.	Mute, unresponsive though seemingly alert, delusions of pregnancy and of abortion.	Dyskinesias. Temp. up to 102.	Abnormal diffuse.	8 WBC, (6 poly) protein, sugar normal.	One month.
10	17	F	Low grade fever, drowsiness, concerned about school work, inappropriately hostile.	Withdrawal, memory defects, disorientation, hostile, hyperactive, denial of deficits, dyscalculia.	Seizures, dyskinesias. Temp. up to 102.	Abnormal bilateral.	20 WBC, (all lymphs).	One month.

rather withdrawn, particularly fearful of sexual advances. Several weeks prior to admission she had a sore throat and fever which cleared spontaneously. Several days prior to admission she began to complain of headache and was unable to sleep. She told her parents that they were "on Mars." She then complained of increased headache and appeared to be unsteady when walking. She then became mute, nodding her head in answer. Still later that day she did not understand commands. She was described as catatonic and was hospitalized. Spinal fluid on admission was normal but on the next day there were 8 leukocytes per cubic millimeter (6 polymorphonuclears and 2 lymphocytes). Electroencephalogram was diffusely abnormal with spikes, basic frequency of 3-5 cps with scattered 1.5-3 cps activity. Intermittent grimacing and fluctuating muscular tone followed. Temperature rose to 102 during the first week. She began to speak after a week and confabulated about being married, of having had an abortion, of having killed a baby. She had cleared by the fourth week and was discharged asymptomatic.

*Case 10.* The patient was a 17 year old college student who was said to have "erratic" behavior with wide mood swings during the previous year. One week before admission she had a mild fever and was slightly drowsy. During the next few days she would make apparently unjustified hostile remarks. She then became withdrawn and extremely hostile toward her family. Two grand mal seizures followed on the day of admission. On admission temperature was 102°. She was described as shouting and restless. Would not follow commands. Kept repeating "mommy, mommy help me, I feel sick." Spinal tap showed 89 RBC; no WBC; protein 48, sugar 78. By the next day she was more alert but continued to be irritable. EEG was abnormal with bilateral irregular 1.5-4 cps activity up to 120 microvolts bilaterally. Repeat spinal tap showed 20 WBC all lymphocytes with protein 41 mg%. Subsequently had several more seizures including one which began with spots in front of eye moving to right with clonic movements of right arm. During this period she was oriented.

Speech was tremulous, slightly dysarthric with tremulous myoclonic movements of right half of body including face. Had nystagmus and a left Babinski. Had difficulty with reversals, serial 7's and calculations. Later became depressed before being discharged a month after onset of illness. There were short and long runs of 3-4 cps spike and wave with irregular 1.5-3 cps activity on EEG just prior to discharge.

#### DISCUSSION

In all these patients (see Table I), aside from Case No. 6, there was an antecedent history of a non-specific febrile illness, usually involving the respiratory tract but involving the GI tract in Case No. 4. Again, aside from Case No. 6 which presented with seizures, the presenting symptoms were "mental" changes prior to other symptoms and signs of involvement of the central nervous system.

The type of behavior which was initially exhibit varied considerably. Hallu-

cinations of various sorts, mainly auditory, were found in Cases No. 1, 3, 4. Delusions and confabulations were found in Cases No. 1, 7, 9. Sexual acting out and violent behavior were seen in Cases No. 2, 5, 8, 10. These symptoms led to initial errors in diagnosis. Indeed, even when other symptoms of involvement of the central nervous system presented, the *pattern of behavior* in many ways could not be distinguished from that of the schizophrenic.

Seizures, dyskinesias, oculogyric crises later appeared, as well as high temperatures. In some, Cases No. 1-4, the temperature consistently rose to the range of 104-107° F. The course usually lasted about 2-3 months before clearing. However, in Case No. 2 persistent behavioral disturbances required more chronic hospitalization and Case No. 9 remains unimproved two and a half years post onset with evidence of severe brain atrophy. The symptomatic use of electro-convulsive therapy was associated with recovery in Cases No. 1, 5 but was not used in other cases which recovered spontaneously. It had no beneficial effect on the course of Case No. 9. Nor were high doses of steroids of value in this case.

The presence of "mental" disturbances in these patients does not appear to be surprising. The relatively acute onset, the severity of the involvement and the apparent involvement of the deeper structures of the brain as evidenced by the high fevers, may all contribute to producing the clinical picture. Of importance is the concept that these so-called "mental" disturbances are but symptoms and need not have particular etiologic significance per se.

They are but symptoms which reflect the presence of brain dysfunction and the particular patient's previous areas of preoccupation and previously preferred modes of adaptation to stress (12). The religious content of the delusions and hallucinations in Case No. 1 may reflect her concern with religion in terms of her religiously mixed marriage and conversion. The compulsive and phobic behavior in Case No. 3 had been her pattern throughout her life. The preoccupation with death and violence in Cases No. 4, 5, 6, 10 may reflect the depression that they had been feeling prior to the illness and the tendency to be withdrawn when under stress.

Particularly striking were the sexual delusions and preoccupations of Cases No. 2, 6, 9. Case No. 8 also had hallucinations about her young nephew and her husband, as well as almost constant masturbation and sexual preoccupations. Her pre-morbid concerns had been in terms of family and sex.

With disturbance of consciousness and the brain dysfunction induced by the inflammatory disease of the brain behavioral changes occur which at times mirror the pre-morbid preoccupations of these patients. One would suggest that more concerted attempts be made in these patients to study their pre-morbid behavior in terms of their preferred modes of behavior.

#### SUMMARY

1. Ten cases of sporadically occurring acute inflammatory disease of the brain which presented with symptoms mimicking psychiatric illness are described.

2. These phenomena may produce initial diagnostic difficulties.
3. The significance of these phenomena as related to the organic brain disease and to the pre-morbid personality is briefly discussed.

## REFERENCES

1. von Economo, C.: *Encephalitis Lethargica; its Sequelae and Treatment*. London: Oxford University Press, 1931.
2. Abrahamson, I.: *Lethargic Encephalitis*. New York: 1935, pp. 32-44.
3. Neal, Josephine B., Ed.: *Encephalitis—a Clinical Study*. New York: Grune & Stratton, 1942. Passim and particularly Rosner, A. A.: *The Psychiatric Sequelae of Epidemic Encephalitis*. pp. 325-359.
4. Jelliffe, S. E.: *The Mental Pictures in Schizophrenia and in Epidemic Encephalitis*. *Am. J. Psychiat.*, 6: 413, 1927.
5. Kirby, G. H., and Davis, T. K.: *Psychiatric Aspects of Epidemic Encephalitis*. *Arch. Neurol. & Psychiat.*, 5: 491, 1921.
6. Lauter, R., Soos, L., and Khene, M.: *Encephalitis Presenting Like a Tumor in the Form of Catatonic Hebephrenia*. *Ann. Med-psychol. (Paris)*, 116: 518, 1956.
7. Heidrich, R., and Wenscher, W.: *Catatonic State in the Course of a Leukoencephalitis*. *Psychiat. Neurol. Med. Psychol. (Lpz)*, 13: 241, 1961.
8. Navian, J., Fouche, F., and Benoit, M.: *Apropos of a Type of Leukoencephalitis with Psychiatric Initial Symptoms*. *Ann. Med-psychol. (Paris)*, 119: 334, 1961.
9. Weinstein, E. A., Linn, L., and Kahn, R. L.: *Encephalitis with the Clinical Picture of Schizophrenia*. *J. Mt. Sinai Hosp.*, 21: 341, 1955.
10. Strauss, H.: *Intracranial Neoplasms Masked as Depressions and Diagnosed with the Aid of Electroencephalography*. *J. Nerv. & Ment. Dis.*, 122: 185, 1955.
11. Olin, H. S., and Weisman, A. D.: *Psychiatric Misdiagnosis in Early Neurologic Disease*. *J.A.M.A.*, 189: 533, 1964.
12. Weinstein, E. A., and Kahn, R. L.: *Denial of Illness: Symbolic and Physiologic Aspects*. Springfield, Ill.: C. C. Thomas, 1955.

# CLINICO-PATHOLOGICAL CONFERENCE

## Unexplained Ascites for One Year

*Edited by*

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A 45 year old Puerto Rican housewife was admitted to The Mount Sinai Hospital because of abdominal fullness and discomfort for four months. This was associated with anorexia, weight loss and several loose bowel movements a day in addition to a low grade fever. She had lived in New York for 29 years but was in Puerto Rico for the last three years. She had two children and 18 years ago had an appendectomy and a tubal ligation. There was no family history or contact with tuberculosis. Two months after the onset of symptoms she was admitted to a hospital in Puerto Rico where right lower quadrant and right adnexal tenderness and ascites were found. At laparotomy small nodules up to 4 mm in diameter were seen over the entire peritoneum. Several liters of ascitic fluid were removed. The liver, stomach, bowel and pancreas appeared normal. Several nodules were biopsied, and a distal segment of the right fallopian tube (Fig. 1). The nodules were reported as areas of mesothelial cells and macrophages with mononuclear cell infiltration. The tube was edematous and congested but contained no leukocytes. Neither granuloma or tumor was seen. Because tuberculosis was felt to be the most likely diagnosis, the patient was given isoniazid and streptomycin. However, the ascites recurred shortly after and necessitated paracentesis. She returned to New York to receive further medical care and was admitted to this hospital.

Her temperature was 99°, pulse 100/min., blood pressure 120/70 and respirations 20/min. She appeared pale and chronically ill. The only significant abnormalities found on physical examination were ascites and a palpable edge of the liver and tip of the spleen.

A small amount of albumin, a few hyaline casts and red blood cells were found in the urine. The hemoglobin was 9.9 G%. The white blood count was 19,500/mm<sup>3</sup> with 72% segmented cells, 1% band forms, 19% lymphocytes and 7% monocytes. The platelet count was 1,285,000/mm<sup>3</sup>. The sedimentation rate was 80 mm/hr. The blood urea nitrogen, creatinine, blood sugar, serum bilirubin, prothrombin time, serum alkaline phosphatase, serum amylase, and serum glutamic oxalacetic transaminase were normal. The serum albumin was 1.7 G% and serum globulin 4.1 G%. Serum electrophoresis showed high gamma and alpha globulins and low albumin. The serum cholesterol was 105 mg% with 70% esters. The serum sodium, and potassium and phosphorus were normal; the CO<sub>2</sub> was 36 mEq/L and the serum calcium 8.2 mg%. During the patient's hospital stay, the serum calcium dropped to as low as 4.0 mg% with-

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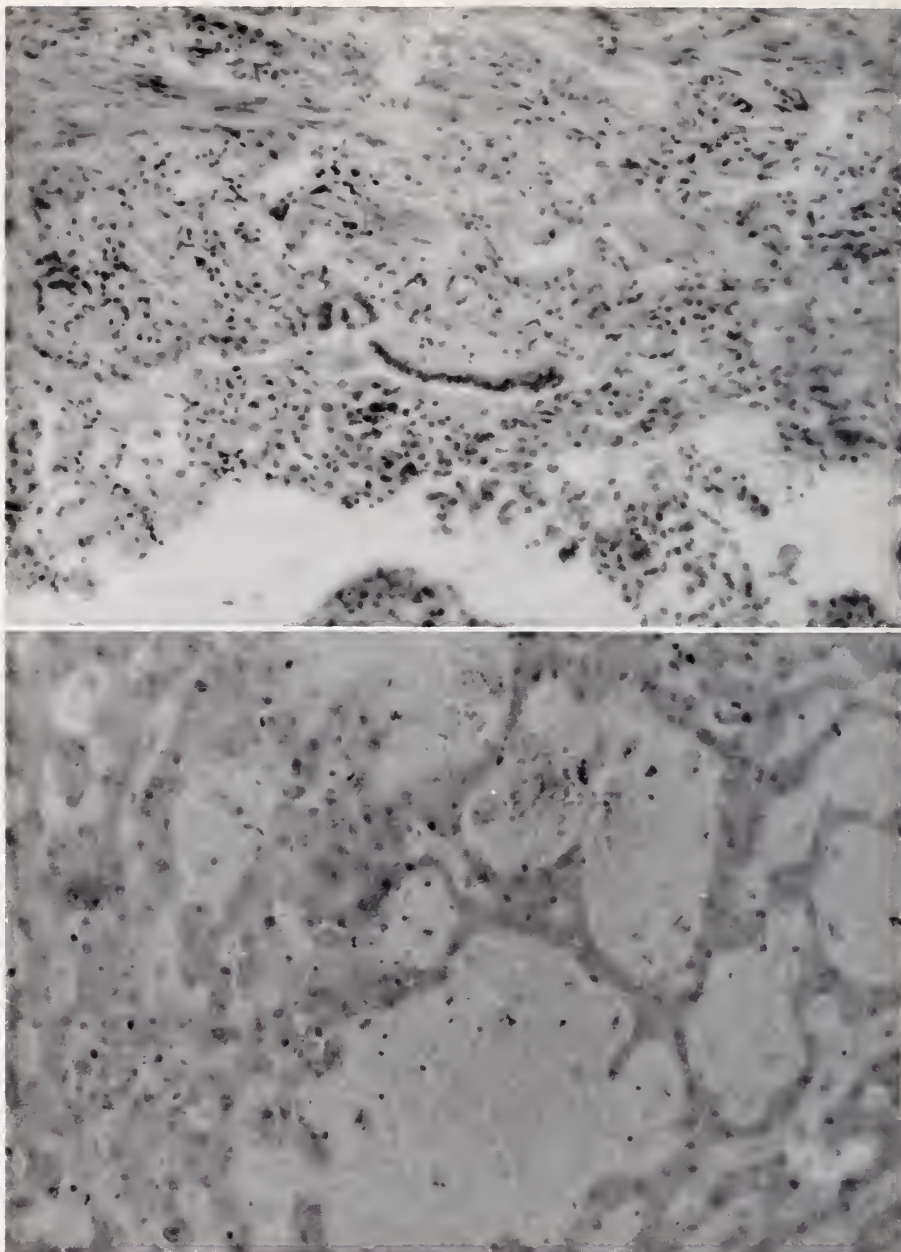


FIG. 1. Biopsy of fallopian tube showing mesothelial cells and chronic inflammation (H & E  $\times 100$ ).

FIG. 2. Peliosis of liver (H & E  $\times 400$ ).



out symptoms. The stools were guaiac negative but contained increased neutral fats. The purified protein derivative second strength was positive. The peritoneal fluid contained mesothelial cells, erythrocytes and leukocytes and 1.7 G% albumin and 2.8 G% globulin. Cultures of the blood, bone marrow and peritoneal fluid were sterile. Biopsies of lymph nodes, small intestine and bone marrow were normal. The chest x-ray indicated blunting of both costophrenic angles and the flat film of the abdomen suggested the presence of ascites.

In the hospital, the patient continued to have a low grade fever despite therapy with isoniazid, streptomycin and para-aminosalicylic acid, and anemia despite blood transfusions. Because of persistent ascites, culdoscopy was performed on the fifteenth hospital day and the whitish nodules were again seen. Biopsy of these revealed hypertrophic mesothelial cells, acute and chronic non-specific inflammation and prominent epithelioid cells. After a month in the hospital she became mildly jaundiced with a peak serum bilirubin of 3.2 mg% and a serum alkaline phosphatase activity of 39.8 King Armstrong units. The serum glutamic oxalacetic transaminase rose to 41 units. These all returned to normal after para-aminosalicylic acid was discontinued. Fever and loose stools continued but sigmoidoscopic examination did not reveal any mucosal changes. Because of the diarrhea a rather severe metabolic hypokalemic alkalosis developed. This responded to appropriate fluid and electrolyte therapy. Prednisone, 40 mg a day, was started after four weeks in the hospital. This decreased but did not eliminate the diarrhea. The patient became distended and dyspneic and paracentesis yielded an odorous purulent fluid, which contained polymorphonuclear leukocytes and anaerobic diplococci. A laparotomy was performed on the forty-third hospital day. The bowel was matted together by a diffuse granular overgrowth which was thought to be a purulent peritonitis resulting from the culdoscopy. Drainage was instituted and she was given penicillin and chloramphenicol. Diarrhea and ascites recurred and did not respond to parenteral neomycin and steroids. She was also continued on isoniazid and streptomycin and pyrazinamide was added. After several weeks she again became jaundiced with a peak bilirubin of 8.0 mg%, serum glutamic oxalacetic transaminase of 92 units and a serum alkaline phosphatase activity of 50.3 King Armstrong units. A biopsy of the liver showed severe cholestasis and ductular proliferation suggesting toxic hepatitis. The jaundice subsided with discontinuation of the pyrazinamide. The patient was given prednisone, albumin, and blood transfusions, large doses of testosterone propionate, supplemental vitamins, calcium gluconate and potassium chloride with no improvement. She gradually lost more weight and became weaker. Stitch abscesses developed in the abdominal wound and drained persistently. Flexion contractures developed in the hips and knees. On the 200th day in the hospital she developed dyspnea, tachycardia and fever with bronchial breathing. She expired three days later failing to respond to antibiotics and digitalis.

*Dr. Henry D. Janowitz\**: This 45 year old Puerto Rican housewife who

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presented with abdominal fullness and discomfort was not a neurotic housewife with chronic functional symptoms for two hundred days later she was dead. Her whole illness had been less than a year's duration.

It is interesting that she had been born in Puerto Rico but lived most of her life in the United States and then became ill in Puerto Rico. I mention this because there were physical findings and laboratory tests suggestive of malabsorption and I wondered whether they were consistent with tropical or non-tropical sprue. As you know, the field has been further complicated by the introduction of the term "temperate sprue" but I do not think that she had one of these three varieties.

It is clear also that the physicians in the first hospital faced exactly the same dilemma and the same therapeutic problems that were faced here. They saw a woman who had ascites and although they quickly obtained an operative specimen, they then were presented with the difficulty of interpreting the peritoneal biopsy.

Is the biopsy specimen available?

*Dr. E. Rubin†*: The fallopian tube showed numerous hyperplastic cells. There was a non-specific inflammation throughout the wall of the tube distally. No fungi or microorganisms could be seen. This was interpreted as a non-specific chronic peritoneal reaction.

*Dr. Janowitz*: Although the biopsy did not provide a microbiologic diagnosis, she was treated for tuberculous peritonitis. She failed to respond to therapy and the ascites reaccumulated requiring paracentesis.

I saw this patient during life but the general physical examination was not helpful. Ascites, of course, was prominent and there was a question of a palpable spleen. There was no peripheral edema.

Most of the studies of the liver were normal, except for a very low serum albumin and a high gamma and alpha globulin.

There were certain other laboratory studies which raise some question concerning intestinal absorption. She had some loose stools and there was increased neutral fat on smear. The serum cholesterol was 105 mg%, the calcium fell as low as 4 mg% and the serum albumin was low. These studies suggest interference with fat digestion and possibly also with fat absorption.

In the course of her 200 days in the hospital she was subjected to a second laparotomy, and a culdoscopy. Three pieces of tissue were obtained and apparently all again revealed the same findings as seen on the previous biopsy specimen.

I am taking at its face value the failure of the surgeons at both laparotomies to find other abnormalities besides the nodules scattered through the peritoneum, and diffuse granular overgrowth at the second operation.

There are three constellations of syndromes in this patient that I wish to discuss.

One was the syndrome of toxic hepatitis and jaundice which she exhibited on two occasions, both related to drugs. Withdrawal of paraaminosalicylic

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acid led to a rapid clearing of the jaundice and a liver biopsy performed after pyrazinamide administration showed intrahepatic cholestasis consistent with a drug hepatitis. I do not think that either of these two episodes elucidates the fundamental disease from which this patient was suffering.

Secondly, I have mentioned the malabsorption syndrome. The features which suggested that there was an element of malabsorption was that she was of Puerto Rican extraction; she had a low serum calcium on one occasion; the stools were fatty, the serum albumin was low and there was sufficient diarrhea to result in an electrolyte imbalance. On the other hand, the x-rays of the small bowel were normal. The peroral Crosby capsule biopsy was also normal and vitamin and prednisone therapy apparently failed to influence her clinical course. If she had malabsorption, it would certainly seem clear that she did not have a primary form of malabsorption, such as idiopathic steatorrhea, adult celiac disease or tropical sprue.

If she had secondary malabsorption, it must have been due to an intra-abdominal disease which apparently did not involve the mucosa. We certainly know that there are sampling errors in small bowel biopsies, but in a disease such as adult celiac disease or the other varieties that I will mention, one ought to get some glimpse of this on the small bowel biopsy. Therefore I do not believe that she was suffering from a mucosal lesion of the small bowel.

I now must grapple with the basic problem. When a patient develops ascites in advance of or without evidence of peripheral edema, one must look for a local intra-abdominal cause. As one scans the list of diseases the first one to be considered is tuberculosis of the peritoneum. The purified protein derivative was positive only in the second strength but this does not rule out active tuberculosis. Although she had been started on therapy, failure to find acid-fast organisms on three biopsies is certainly against tuberculosis. While it is risky to make a differential diagnosis based on the response to therapy, in this case the therapeutic response was uniformly disappointing. I think it is unlikely that this patient had the disease for which she was treated vigorously.

When I read the abstract and learned about the mesothelial cells and acute and non-specific inflammation and epithelial cells, I also thought of Hansen's disease, but I never heard of Hansen's disease confined to the peritoneum, and I should think that these macrophages would have been loaded with acid-fast bacilli. Therefore I must eliminate this specific form of infection.

One then thinks of portal hypertension with or without liver disease as a cause of persistent ascites. If she had portal hypertension, the cause was not obvious. The common clinical findings and abnormal liver function tests of Laennec's cirrhosis or portal cirrhosis were not present. The patient's course was also against that of portal hypertension. There was no evidence of congestive splenomegaly or hypersplenism. Indeed I find it difficult to understand why she had so many platelets. I assume the liver biopsy specimen would have shown evidence of cirrhosis if it had been present, although I am sure a sampling error is possible.

Other forms of portal hypertension do not seem to be applicable in the

present situation. If she did have portal hypertension, the low serum albumin in the absence of liver disease would have to be explained.

Since she came from Puerto Rico, she could have had portal hypertension due to schistosomiasis of the liver. The liver function tests are consistent with this diagnosis and on liver biopsy the characteristic granulomas may be missed. The course is not consistent with schistosomiasis, so that I am very uncomfortable ascribing her ascites to portal hypertension and intrinsic liver disease. Furthermore, the liver was described as normal at the first exploration.

In addition, one has to think of mechanisms that prevent the outflow or egress of lymph from the abdominal cavity. If the ascites were chylous, one would think of retroperitoneal lymph node involvement with invasion of the lymphatic channels.

I come next to the last in the large category of infectious and mechanical or obstructive lesions. I dismiss carcinoma of the pancreas. Ovarian carcinomas are notorious for seeding the peritoneum and causing ascites. She was explored on two occasions and carcinoma was not found.

We do not have any evidence upon which to make a diagnosis of other metastatic lesions.

There are some other interesting lesions of the peritoneum which usually lead to an accumulation of mucinous fluid. Pseudo-myxoma peritonii is one. It may arise from a mucocoele of the appendix, and there was an interesting report last year of mucinous fluid involving the entire peritoneum.

Since this is a Clinical-Pathological-Conference, I considered the possibility that the macrophages contained PAS staining material. Where any special stains done?

*Dr. Rubin:* Initially we just looked for bacteria.

*Dr. Janowitz:* I raise the question since a variant of Whipple's disease could be possible. However, she was a woman which somewhat lessens the chances. The small bowel biopsy was normal and I have never heard of a case terminating precisely in this fashion.

Although the lesions did not look like granulomas, one has to consider Boeck's sarcoid. The chest film was normal but the globulins were elevated. There was no evidence to suggest Boeck's sarcoid except the small peritoneal nodules, but I am not aware of any patient in which ascites was the sole manifestation. She also did not respond to steroids.

There are other unusual diseases in which there are collections of macrophages, sometimes containing lipoidal material. It is conventional to list them under the title of histiocytosis-X. As I understand it, there are combinations of Hands-Schuller-Christian's and Lederer-Siewe's disease but they have multiple system involvement including bone and lung.

Based on the fact that there were mesothelial cells seen on the biopsy and that there was a persistent accumulation of ascites which failed to respond to specific anti-bacterial agents and steroids, I would like to suggest a diagnosis of mesothelioma, a malignant tumor of the mesothelial cells. Although it is



more commonly seen in the pleura, on occasion it may be isolated to the peritoneum.

*Dr. Rubin:* Are there any questions for Dr. Janowitz?

*Question:* In the presence of a normal bowel could the presence of fluid in the peritoneum mechanically cause such a condition?

*Dr. Janowitz:* In constrictive pericarditis there may be a protein leak presumably from dilated lacteals of the small bowel, but evidence of gross malabsorption in constrictive pericarditis is extremely rare, and I did not consider it.

*Question:* Can cirrhosis of the liver with ascites or tumor implants of the mesentery produce malabsorption?

*Dr. Janowitz:* There is some evidence for impaired absorption in patients who have portal hypertension and Laennec's cirrhosis. There has been a considerable debate as to whether this is due to disease of the small bowel or to failure of fat digestion, due to bile insufficiency. The biopsy of the small bowel usually shows a normal mucosa in cirrhosis. The few cases of ascites resulting from ovarian carcinoma really do not have evidence of malabsorption, unless lymph nodes are involved, as is seen in lymphosarcoma with lymphatic obstruction.

*Dr. Rubin:* The lungs were entirely airless. They were very firm, fleshy and weighed about four times normal. Microscopically within all of the alveoli were collections of polymorphonuclear leucocytes. She died of bronchopneumonia, the terminal event of a cachectic course.

The heart showed further evidence of the chronic debilitating nature of her disease. It was small and exceedingly brown; the so-called brown atrophy of the heart, which we generally associate with extreme old age or a debilitating disease.

The spleen was slightly enlarged and was covered by a grayish-white material. On section it contained large amounts of iron, a result of the blood transfusions she received.

The surface of the liver also displayed a grayish-white material which could be easily removed. The cut surface had an accentuated lobular pattern and there were numerous small reddish areas present in multiple parallel sections.

In portal tracts, there was proliferation of small bile ductules and some fibers, suggesting that the insult to the liver was of some duration. There was no cirrhosis and no disruption of the lobular architecture.

The presence of binucleated, hyperchromatic cells was evidence of a minor but prolonged hepatic regeneration in response to injury and was further evidence that the insult to the liver was prolonged.

Bile was present in dilated canaliculi. These bile thrombi, together with the enlarged portal tracts, represented a cholestatic toxic hepatitis, probably on the basis of drug therapy.

The small red areas seen grossly were dilated sinusoids which had actually

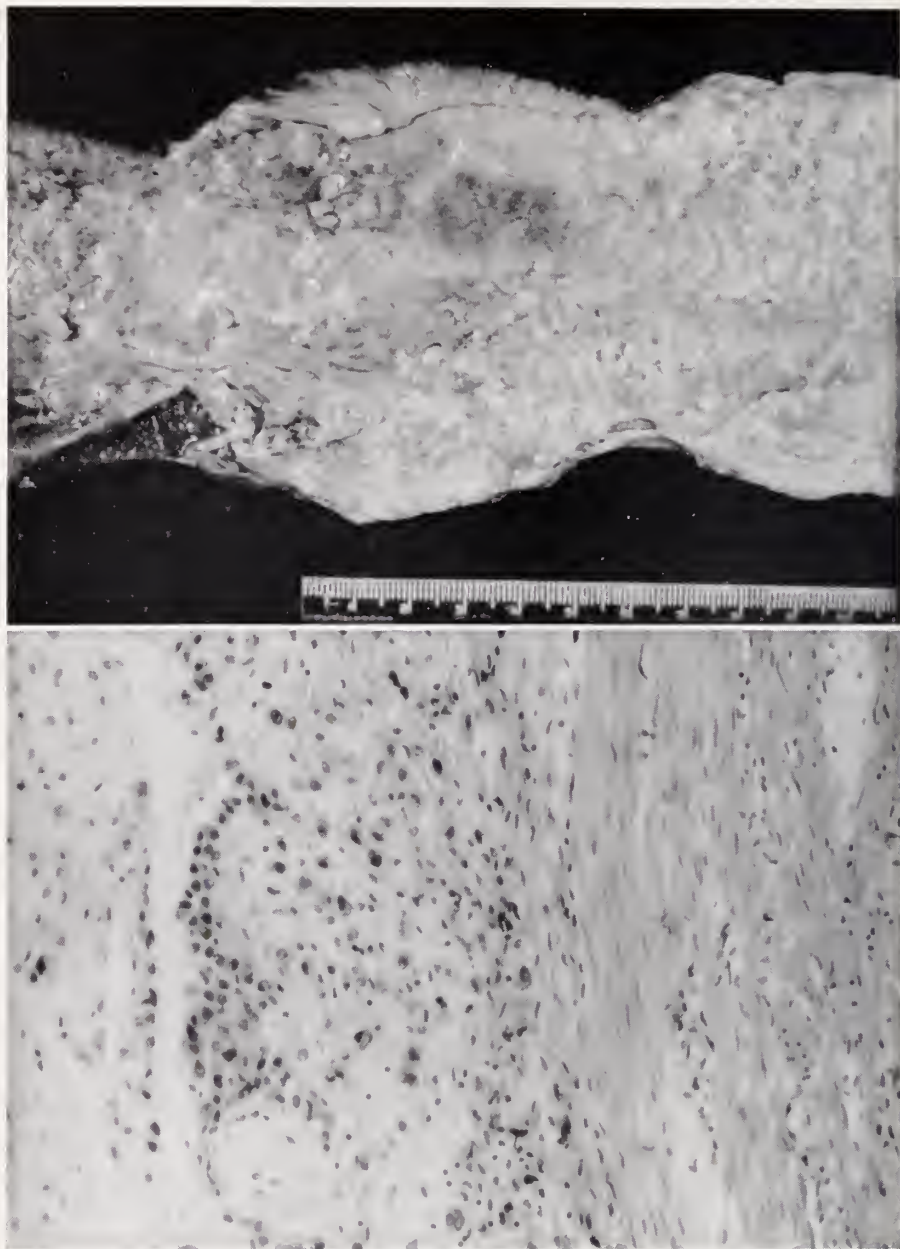


FIG. 3. Serosal surface of small bowel showing numerous small nodules.

FIG. 4. Microscopic section from area shown in previous figure. Note chronic inflammation and hyperplastic mesothelial cells (H & E  $\times 100$ ).



become large blood containing vessels (Fig. 2). No endothelial lining was present and they resembled cavernous sinuses lined by liver cells. This was peliosis of the liver. Peliosis of the liver has been associated with administration of anabolic steroids (1), and with fibrosing peritonitis (2). This woman received testosterone and had peritonitis but a causal relation is not definite.

Large, soft plaques occupied a large part of the peritoneal-omental surface and could be scraped off the surface (Fig. 3). They were also present over the pelvic organs.

The entire serosal surface of the small bowel resembled a chronic fibrosing peritonitis.

Grossly, it was difficult to decide whether this was an infectious or neoplastic process.

Microscopically, mesothelial cells were not just on the surface of the peritoneum but were within the substance of the mesentery. The cells were large, and numerous inflammatory cells were also scattered throughout the peritoneum. In areas there were bizarre clefts lined by these large cells.

The serosal surface of the small bowel and the mesentery had a chronic peritonitis (Fig. 4) but within the peritonitis was the same cleft formation and lining cells arranged in a palisade form (Fig. 5).

The diaphragm also had on its surface the same type of lining and inflammatory cells. We are confronted with a process which did not extend beyond the abdominal cavity but which involved all of the serosal surfaces.

These cells had large basophilic cytoplasm, vesicular nuclei and very prominent nucleoli. They did not resemble inflammatory cells; nor were they ordinary hyperplastic mesothelial cells. They appeared neoplastic.

To confirm our suspicions, more sections were taken and bizarre patterns with fronds, papillary formation and infiltration of the serosa were seen (Fig. 6).

This was a peritoneal mesothelioma, a rare tumor. About 30 cases have been reported in the world literature.\* Certain criteria are necessary for diagnosis. It is restricted to the abdominal cavity, although three cases have been reported which involved the pleural cavity by direct extension (4).

The course should be prolonged with progressive disability and ascites which eventually leads to the patient's demise. Most such patients, however, die of bronchopneumonia, as this patient did.

Pathologically, the tumor has a characteristic appearance—that is, it remains on the serosal aspect of the abdominal viscera. The growth is progressive and microscopically various patterns can be seen. In this case we saw two patterns. In one, many clefts were lined by hyperplastic mesothelial cells which were actually neoplastic. The other pattern was diffuse infiltration with single cells. This neoplasm may appear as a fibroblastic or spindle cell tumor. At times it may resemble an adenocarcinoma although closer examination will usually reveal that there is no true gland formation.

\* Note: Since this Clinical-Pathological Conference, many more peritoneal mesotheliomas have been reported associated with asbestosis (3, 4).

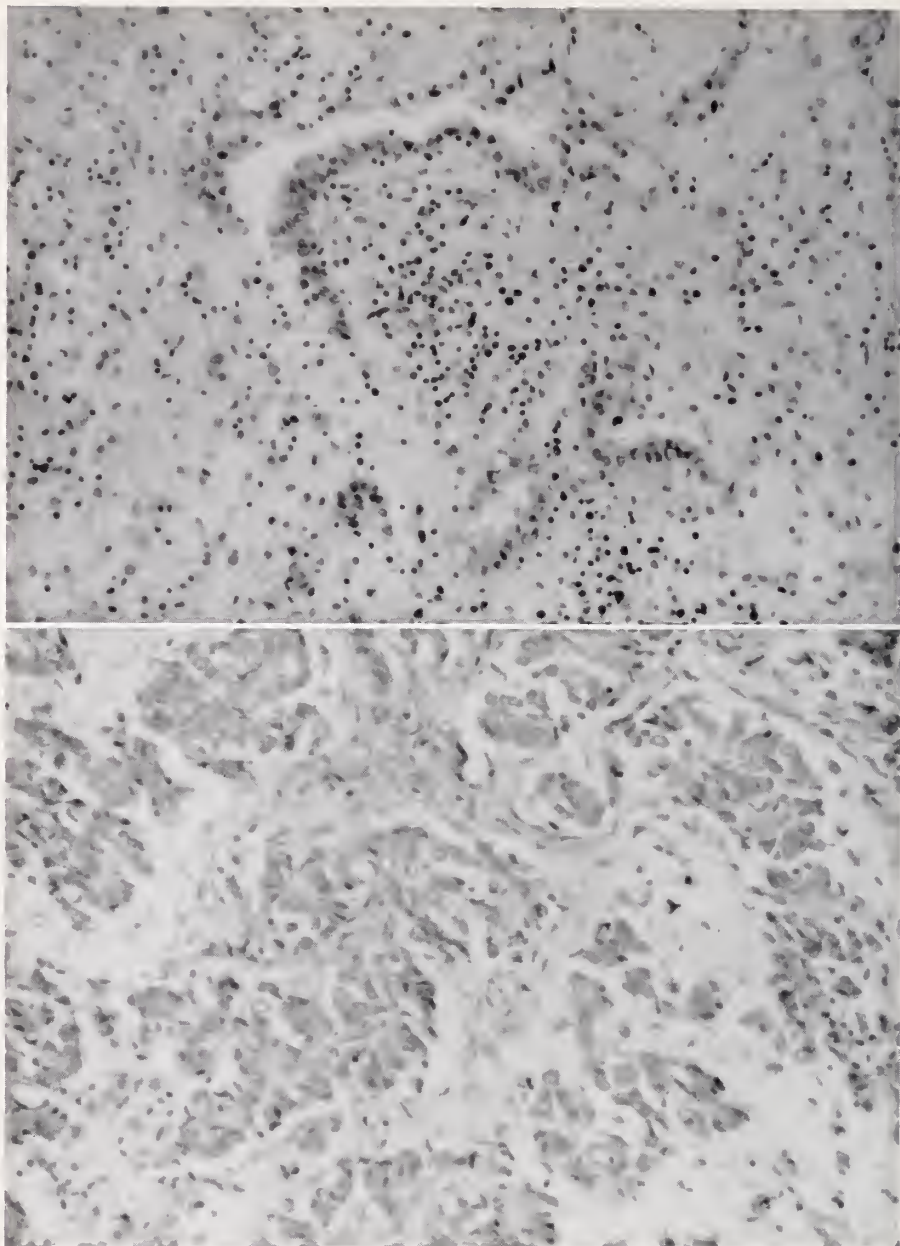


FIG. 5. Section from mesentery showing clefts lined by mesothelial cells (H & E  $\times 100$ ).

FIG. 6. Section from omentum showing papillary frond-like arrangement of tumor (H & E  $\times 200$ ).

Metastases are uncommon, but lymph nodes are involved in about one half of the cases. Most of the patients are males over 40 years of age but about seven cases have been reported in females.

The diagnosis can be extremely difficult even in the presence of tissue biopsies. In the largest series of cases reported by Winslow (4), they were able to demonstrate in proved cases of peritoneal mesothelioma transitions between normal mesothelial cells, hyperplastic and frankly neoplastic cells.

In all three biopsies the pathologists were confronted with a relatively non-specific picture which could occur in almost any type of a chronic peritonitis.

#### *Final Diagnoses:*

1. PERITONEAL MESOTHELIOMA
2. TOXIC HEPATITIS
3. PELIOSIS OF LIVER
4. BRONCHOPNEUMONIA

#### REFERENCES

1. Gordon, B. S., Wolf, J., Krause, T., and Shai, F.: Peliosis Hepatitis and Cholestasis Following Administration of Norethandrolone. *Amer. J. Clin. Path.*, 33: 156, 1960.
2. Hamilton, F. T., and Lubitz, J. L.: Peliosis Hepatitis. Report of Three Cases, with Discussion of Pathogenesis. *Arch. Path.*, 54: 564, 1952.
3. Selikoff, I. J., Churg, J. and Hammond, E. C.: Relation between Exposure to Asbestos and Mesothelioma. *New Eng. J. Med.*, 272: 560, 1965.
4. Churg, J., Rosen, S. H., and Moolten, S.: Histological Characteristics of Mesothelioma Associated with Asbestos. *Ann. N.Y. Acad. Sc.*, in press.
5. Winslow, D. J., and Taylor, H. B.: Malignant Peritoneal Mesothelioma. A Clinicopathological Analysis of 12 Fatal Cases. *Cancer*, 13: 127, 1960.

## RADIOLOGICAL NOTES

CLAUDE BLOCH, M.D., AND HARVEY M. PECK, M.D., Co-Editors

*New York, N. Y.*

### CASE NO. 258

This 82 year old male was admitted to the hospital because of the presence of an abdominal mass. The patient was asymptomatic in that he had no abdominal pain, anorexia, weight loss or constipation.

Physical examination revealed a grapefruit-sized, slightly tender mass in the right side of the lower abdomen. There was no evidence of hepatomegaly or splenomegaly. There were no enlarged peripheral lymph nodes.

Laboratory examination revealed a hemoglobin of 7 Gm per cent, an elevated sedimentation rate and a 4 plus guaic positive stools.

Barium enema was performed which revealed a large mass in the cecal region (Fig. 1A, arrow A) with an area of ulceration within its lateral portion (Fig. 1A, arrow C). The mass was noted to extend across the midline and to displace the mid-sigmoid colon to the left (Fig. 1A, arrow B).

Pressure spot films of the cecal region confirmed the presence of an irregular shallow ulceration (Figs. 1B and 1C). Nodularity was noted along the edges of the ulcer and within the base of the ulceration. The terminal ileum filled by reflux (Fig. 1C), and appears to be normal in caliber. The lesion was noted to extend to the ileo-cecal valve.

Because of the findings on the barium enema, a laparotomy was performed which revealed a large neoplasm in the cecum. It occupied the caput coli and contained a flat, nodular ulceration. An ileo-colic resection was performed with an ileo-transverse colostomy. The mass was adherent to the sigmoid but did not invade that portion of the colon. The ileum appeared normal. The right ureter was dissected free from the mass. The specimen revealed a grapefruit-sized mass, and the ulceration measured 7 cm in diameter. Numerous enlarged nodes were noted within the mesentery. Microscopic diagnosis of both the tumor and the lymph nodes was lymphosarcoma. The patient made an uneventful recovery.

### DISCUSSION

Colonic involvement in lymphosarcoma is rare and may exist as a localized ulcerating mass, as in the present case, or more rarely as a diffuse submucosal infiltration of the large intestine (1). Although it is difficult to differentiate the isolated lesion of lymphosarcoma from carcinomas, the presence of a large bulky lesion with a shallow bizarre ulceration should suggest the correct diagnosis. In cecal lesions, direct involvement of the terminal ileum is more fre-

From the Department of Radiology, The Mount Sinai Hospital, New York, New York.



Case 258, Fig. 1A. Barium enema examination reveals a mass arising in the cecum (arrow A) with a shallow ulceration at the caput coli (arrow C). The mass extends across the midline and displaces the sigmoid to the left (arrow B). The terminal ileum is not filled with barium.





Case 258, Fib. 1B. Pressure spot films of the cecum confirms the presence of a shallow ulceration (between arrows). The ulcer appears to be nodular along its edges and throughout its base.

Case 258, Fig. 1C. The ulcer is again well seen within the mass, and the terminal ileum which is filled with barium appears to enter the mass on its medial aspect (arrow). The ileum is not dilated.

quent than in carcinoma. Because of the lack of desmoplastic reaction in lymphosarcoma, narrowing of the lumen and intestinal obstruction are rare.

Case Report: LYMPHOSARCOMA OF THE CECUM.

#### ACKNOWLEDGMENT

The editors wish to thank Drs. Kaufman Wallach and Albert S. Lyons for permission to publish this case.

#### REFERENCES

1. Wolf, B. S., and Marshak, R. H.: Roentgen Features of Diffuse Lymphosarcoma of the Colon. *Radiology*, 75: 733, 1960.

#### CASE NO. 259

*Submitted by Dr. Murray G. Baron*

This 60 year old male was admitted to the hospital with an 8 month history of dull peri-umbilical pain of a progressive nature. The pain radiated to the back and was not related to food intake. There was no associated nausea, vomiting or anorexia. There was no weight loss or jaundice.

Physical examination was negative and abdominal palpation revealed no masses or enlarged organs.

Laboratory examination revealed a normal hemogram and urinalysis and normal liver profile. Secretin tests of pancreatic function suggested a pancreatic carcinoma.

Oral cholecystography revealed a normal gallbladder. Three separate gastrointestinal series were performed, and although there was irritability of the antrum and duodenal bulb, there were no intrinsic abnormalities and no Roentgen evidence of a mass in the head of the pancreas (Fig. 1A).

Because of the typical pain pattern suggesting a carcinoma of the pancreas together with the positive secretin test, it was decided to perform a selective celiac angiogram. There was good filling of the celiac axis. It was noted that there were at least two definite areas of narrowing in the gastroduodenal branch of the hepatic artery. The artery itself was somewhat displaced in an arcuate fashion, and just immediately superior and lateral to it, a tumor stain was noted (Fig. 1B).

Because of the angiographic evidence, an exploratory laparotomy was performed, and an infiltrating carcinoma of the head of the pancreas was noted.

#### DISCUSSION

Because of the inability to opacify the pancreatic parenchyma, radiologic study of this organ has been largely limited to those lesions that extend outside the normal boundaries of the pancreas. These lesions are detected indirectly by their affect on adjacent structures such as the duodenal sweep or the stomach. In general, these lesions must be relatively large and often are far advanced before they can be detected. Opacification of the pancreatic blood vessels allows us to study the internal structure of the pancreas to some extent and help detect some earlier neoplasms.



As the blood supply of the pancreas is derived both from the celiac and superior mesenteric arteries, it is usually necessary to opacify both of these vessels to completely study the pancreas. The technique of selective celiac arteriography is not difficult. A radiopaque polyethylene catheter with a curved tip is inserted percutaneously into the femoral artery as described by Seldinger. The catheter is then advanced under fluoroscopic control to the region of T12-L1, the curved tip is directed anteriorly and the catheter manipulated until it enters the celiac artery. Following the injection of this vessel the catheter is disengaged and moved slightly distally until it enters the orifice of the superior mesenteric where a second injection is made. These two vessels can be injected simultaneously by passing a second catheter through the opposite femoral artery.

In the case presented, numerous gastrointestinal series were performed and there were only functional changes noted in the antrum and the duodenal bulb which were nonspecific and insufficient to suggest the presence of a pancreatic lesion (Fig. 1A). Opacification of the celiac artery and its branches, however, indicated quite clearly the presence of a carcinoma in the head of the pancreas. Malignant lesions of the pancreas infiltrate the parenchyma and therefore do not produce much displacement of the intrapancreatic vessels as do benign lesions such as pseudocysts. The infiltrating tumor grows around the vessels, irregularly constricting and distorting them. Such variation in the caliber of the vessel (Fig. 1B  $\leftrightarrow$ ) is definitely abnormal and is the most common angiographic sign of malignancy in the pancreas. Another common finding is the presence of abnormal new vessels within the tumor, giving the appearance of a "stain." (Fig. 1B arrow). Early venous filling can also be seen through the tumor bed.

Insufficient experience has been accumulated with pancreatic arteriography to allow an accurate evaluation of its ultimate role as a diagnostic tool in the study of pancreatic lesions. Pancreatic carcinomas can be detected by this method and benign pancreatic lesions differentiated. However, how much more sensitive this technique will be over the barium study of the stomach and small bowel and whether this will be sufficient to warrant the increased time

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Case 259, Fig. 1A. Gastrointestinal series reveals no evidence of a mass in the head of the pancreas. There are some functional changes in the antrum and duodenal bulb.

Case 259, Fig. 1B. Selective celiac arteriogram, frontal view. The catheter has been passed percutaneously through the right femoral artery and advanced through the lumbar aorta (cath) into the celiac axis. The three major branches of the celiac are well visualized (H-hepatic artery, LG-left gastric artery, SP-splenic artery). The dorsal pancreatic artery (DP) arises from the hepatic and ramifies in the body of the pancreas. The gastroduodenal artery (GD) also arises from the hepatic and gives off the superior pancreaticoduodenal artery (SPD) before it becomes continuous with the right gastro-epiploic (RGE). Two areas of narrowing of the gastroduodenal artery are seen ( $\leftrightarrow$ ) in relation to a group of small, irregular new vessels ( $\leftarrow$ ). These indicate the presence of an infiltrating lesion in the head of the pancreas.

and effort involved in the procedure and its increased morbidity, no matter how small, is not known.

*Case Report:* CARCINOMA OF THE PANCREAS DEMONSTRATED BY SELECTIVE CELIAC ANGIOGRAPHY.

#### ACKNOWLEDGMENT

The editors wish to thank Drs. J. Lawrence Werther, Henry D. Janowitz, and Arthur Aufses, Jr., for permission to publish this case.

#### CASE NO. 260

*Submitted by Dr. Louis Brinn*

The patient, a 71 year old female, was discovered to have an anemia four months prior to her hospital admission. Several weeks before admission, there was the onset of sharp, nonradiating, lower abdominal pain not related to meals. Soon after this, constipation was noted. The patient also began to experience nausea, vomiting and fecal eructations. There was an 8 pound weight loss.

Examination revealed a marked fecal odor to the patient's breath. The heart and lungs were unremarkable. A large upper abdominal mass was felt. There was no hepatomegaly or splenomegaly. Rectal examination was negative. A marked anemia was noted. Barium enema at this time showed an irregular narrowed channel in the transverse colon with evidence of nodulation. There was destruction of the mucosa in this region. Barium also outlined a fistulous tract extending to the region of the greater curvature of the stomach. There was evidence of a large soft tissue mass (Fig. 1). The impression was that of a large carcinoma of the transverse colon with fistulization into the stomach.

At exploration, a deeply infiltrating adenocarcinoma of the transverse colon with a fistula into the stomach was found. Much of the tumor was present as a large extra colonic mass which was extensively necrotic and at the same time invading the stomach, this combination of factors resulting in a fistula. A subtotal gastrectomy (Billroth I) and an ileotransverse colectomy were performed, as was a gastrostomy.

#### DISCUSSION

Gastrocolic fistulas primarily result from perforation of gastric or colonic carcinomas, usually of an advanced stage (1, 2). Most series of cases list carcinoma of the colon as a more likely cause of gastrocolic fistula than gastric carcinoma (2, 3). Other etiologies such as benign gastric ulcer with or without previous ulcer surgery, ulcerative colitis, tuberculosis, regional ileitis, pancreatic neoplasms, radiation damage and trauma can produce these fistulas but are less common (1, 4, 5). It should be noted that gastrocolic fistulas differ significantly in etiology from gastrojejunocolic fistulas which almost always are nonmalignant. Gastrojejunocolic fistulas occur in the vast majority



of cases from perforation of a marginal ulcer after previous surgery, gastroenterostomy or less commonly subtotal gastrectomy, for duodenal ulcer (1, 2, 3).

Fecal cruetation or vomiting, weight loss and diarrhea are the classical symptoms indicating a fistula between the stomach and the colon. The patient



Case 260, Fig. 1. Barium enema reveals a constricting carcinoma of the mid-transverse colon (lower arrow) with overhanging edges and destroyed mucosa. An irregular, narrow fistulous tract (upper arrow) is noted to extend through a mass into the stomach. The barium outlining the stomach entered via the fistulous tract.

described above did not have diarrhea apparently because the colon carcinoma was causing a low-grade obstruction. The barium enema examination is much more reliable for demonstrating gastrocolic fistulas, or even gastrojejunoecolic fistulas, than is the barium meal (2, 3, 6, 7). Gastrointestinal series may fail to demonstrate such fistulas in over half the cases. At times it may be difficult to differentiate gastrocolic from gastrojejunoecolic fistulas on barium study. The visualization on barium enema of an obstruction in the transverse colon with fistulization to the stomach is highly indicative of a malignancy, as be-

nign processes causing fistulization are not usually associated with colonic obstruction.

*Case Report: CARCINOMA OF TRANSVERSE COLON WITH GASTROCOLIC FISTULA.*

#### ACKNOWLEDGMENT

The editors wish to thank Drs. Albert Cornell and Bernard Friedman for permission to publish this case.

#### REFERENCES

1. Amlicke, J., and Ponka, J.: Gastrocolic and Gastrojejunocolic Fistulas. *Am. J. Surg.*, 107: 744, 1964.
2. Thoeny, R., Hodgson, J., and Scudamore, H.: The Roentgenologic Diagnosis of Gastrocolic and Gastrojejunocolic Fistulas. *Am. J. Roentgenol.*, 83: 876, 1960.
3. Marshall, S., and Knud-Hansen, J.: Gastrojejunocolic and Gastrocolic Fistulas. *Ann. Surg.*, 145: 770, 1957.
4. Altchek, M., and Summer, P.: Ulcerative Colitis Complicated by Cologastric Fistula. *Gastroenterology*, 33: 823, 1957.
5. Gray, J.: Gastrocolic Fistula Resulting from Benign Gastric Ulcer. *Surgery*, 40: 408, 1956.
6. Schweitzer, R., and Osborne, M.: Gastrocolic Fistula Complicating Carcinoma. *Am. J. Surg.*, 85: 775, 1953.
7. Mark, L.: Diagnosis of Gastrocolic and Gastrojejunocolic Fistulas. *Postgrad. Med.*, 27: 222, 1960.

#### CASE NO. 261

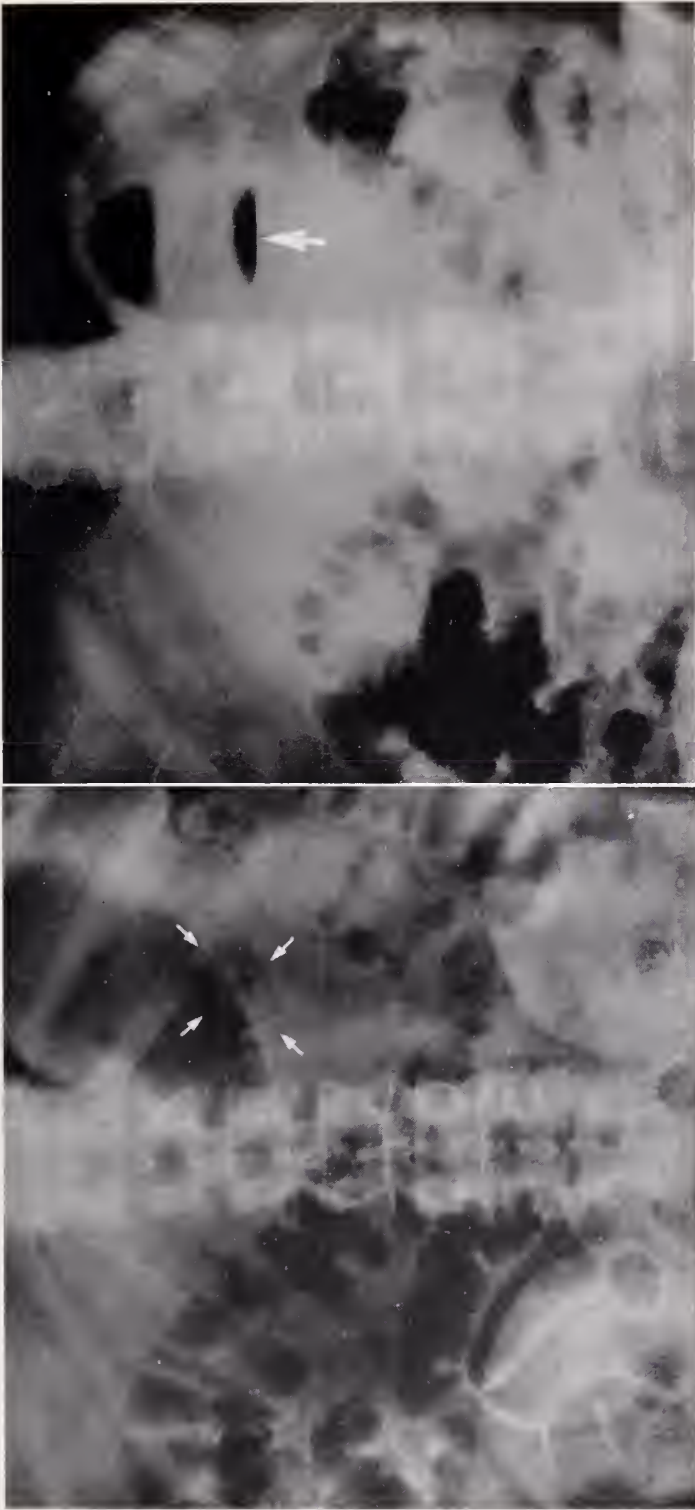
*Case Submitted by Dr. Carl W. Scheer*

A 73 year old white male was in good health until four weeks before admission when he suffered severe, persistent midepigastriaic pain with vomiting, hiccups, and fever. He was admitted to another hospital, where a diagnosis of acute pancreatitis was confirmed by laboratory studies. In spite of conservative therapy, including antibiotics, his symptoms persisted, and he transferred to The Mount Sinai Hospital.

On admission, physical examination disclosed a left upper quadrant tender mass, hyperactive bowel sounds, and a fever ranging between 101°F. and 103°F. Radiographic examination disclosed several small and medium sized gas bubbles in the left upper quadrant lying outside the gut within a large soft tissue mass (Fig. 1A and 1B). Barium meal examination showed the gas-containing mass to be displacing the stomach anteriorly, and the ligament of Treitz caudad (Fig. 1C and 1D). The splenic flexure was displaced downward. The impression was that of a gas-containing pancreatic abscess, or abscess of the lesser sac of pancreatic origin.

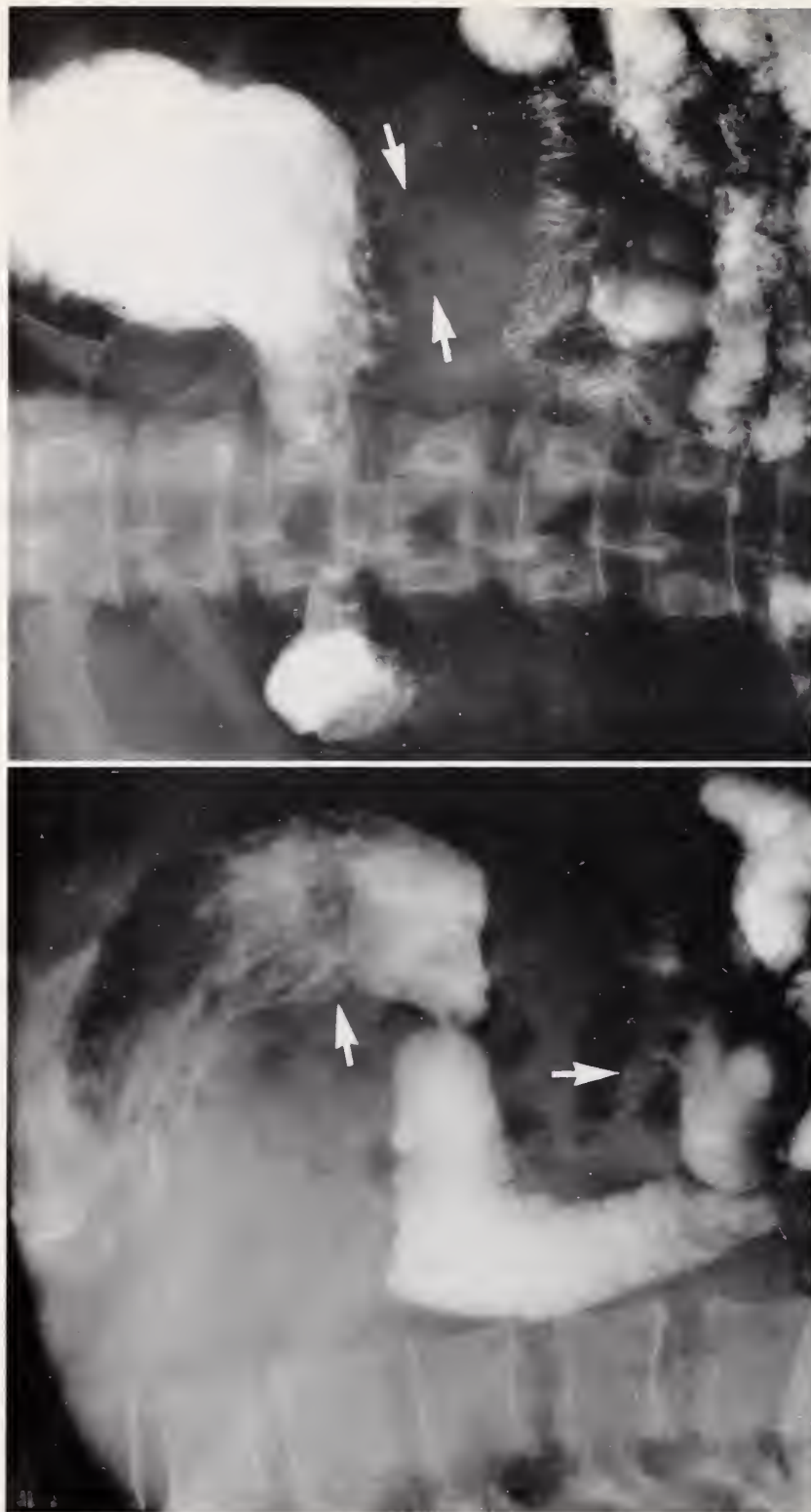
Laparotomy was performed, and a large abscess with thick pus was encountered in the body and tail of the pancreas. Within the abscess cavity were necrotic pieces of pancreatic tissue. Drainage of the abscess was performed. The culture revealed *E. coli*.

Postoperatively, the patient had spiking fevers, elevated blood urea nitrogen, and drainage of a bloody, high-amylase containing serous, and occasion-



Case 261, Fig. 1A. Preliminary film of the abdomen reveals several small and medium sized gas bubbles in the upper quadrant (between arrows) just below the stomach and above the colon. These appear to lie outside the gut within a large soft tissue mass.

Case 261, Fig. 1B. In the upright projection, there appears to be an air fluid level in this same region (arrow).



Case 261, Fig. 1C. Barium meal examination in the lateral projection shows that the gas-containing mass displaces the stomach anteriorly (upper arrow) and the ligament of Treitz inferiorly (lower arrow).  
 Case 261, Fig. 1D. In the frontal projection, the gas bubbles are seen again (between arrows) between the greater curvature aspect of the fundus and the depressed ligament of Treitz.



ally purulent, material from the incisional wound. Cultures continued to grow *E. coli* on occasion.

#### DISCUSSION

The roentgen manifestations of acute pancreatitis have been extensively described in the literature. Findings include separation of the stomach from transverse colon, obliteration of the left upper psoas margin, sentinel loop of the colon, basal pleural effusion, and poorly defined scattered areas of increased density in the abdomen representing areas of saponification. The latter is more often associated with a more chronic form of the disease. Occasionally, a pancreatic abscess may form and localize in the lesser sac, subphrenic area, gastrocolic ligament, pericecal region or psoas area, or it may penetrate the diaphragm to give an empyema (1, 2).

Six cases of acute pancreatitis with gas-containing abscesses, an uncommon complication, were described by Felson (3). These were indistinguishable clinically from pancreatitis without abscess formation. On X-ray examination, the distribution of gas varied, being throughout the pancreas in some cases, and localized in others. In 4 out of 5 pathologically proven cases, the abscess was found to involve the lesser sac. Cultures were performed in only 2 cases, one sterile and one *E. coli*. The X-ray findings in the 6 cases corresponded closely to those found in the propositus, and included gas bubbles behind the stomach; displacement of the stomach anteriorly, ligament of Treitz downward, and splenic flexure downward; ileus; absent psoas shadow on the left; altered mucosal pattern of the distal duodenum.

The diagnosis of gas-containing pancreatic abscess should be strongly suspected by the characteristic amorphous bubbles of gas which are demonstrated to lie outside of the GI tract by appropriate barium studies. The location in the left upper quadrant behind the stomach and the displacement of the ligament of Treitz should localize the abscess to the pancreas or lesser sac.

*Case Report:* GAS-CONTAINING PANCREATIC ABSCESS.

#### ACKNOWLEDGMENT

The editors wish to thank Drs. Lawrence I. Schwartz and Samuel H. Klein for permission to publish this case.

#### REFERENCES

1. Poppel, Maxwell: The Roentgen Manifestations of Relapsing Pancreatitis. *Radiology*, 62: 514, 1954.
2. Weens, H. Stephen, and Walker, Lewis A.: The Radiologic Diagnosis of Acute Cholecystitis and Pancreatitis. *The Radiological Clinics of North America*, Vol. II No. 1, pp. 89-106.
3. Felson, B.: Gas Abscess of the Pancreas, *J.A.M.A.*, 163: 637, 1957.



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## Spontaneous Perforation of the Esophagus: A Report of Four Consecutive Successfully Treated Cases

GUISEPPI ROSSI, M.D., AND DAVID A. DREILING, M.D.

*New York, N. Y.*

The diagnosis of spontaneous rupture of the esophagus is being made with increasing frequency on clinical grounds. Despite reported surgical cures, morbidity and mortality are still very high for a disease that is essentially benign. This is a report on four consecutive cases successfully treated by surgery.

### CASE NO. 1

A 46 year old white male was seen in the emergency room on 11/7/62, five hours after the sudden onset of severe substernal and epigastric pain with vomiting. The patient gave a history of occasional heavy drinking, including the evening before the onset of his illness. Blood pressure was 100/80, pulse rate 100, temperature 98°F., white blood cell count 14,000 and amylase 160 Somogyi units. X-rays of the abdomen and chest were reported as negative. A line of retrocardiac density in the left side was described. The patient had marked upper abdominal involuntary rigidity and tenderness. A laparotomy was performed 5 hours after admission. A small amount of clear fluid and some retrograde gastric edema was found. The pancreas appeared normal. Following operation, the patient went into a state of shock requiring blood transfusions and vasopressors for the next 2 days. On the second postoperative day 1000 cc of straw-colored fluid were aspirated from the right chest. Many pus cells and amylase activity of 715 Somogyi units were found on examination of this fluid. On the third postoperative day an intercostal tube was inserted to treat a hydropneumothorax present on the right side. On the fourth postoperative day the patient had stable vital signs, a temperature of 104°F., but was slightly confused. Hydropneumothorax was still present in the right side. Barium swallow showed extravasation of contrast medium into the right pleura (Fig. 1). Exploration through a right thoracotomy revealed a 2 × 2 cm old perforation of the right wall of the esophagus 1 inch above the diaphragm. The lung was compressed and encased in a thick, soft, fibrinous coat. A large amount of bile-stained fluid filled the right pleural space. Decortication was done and the perforation closed with chromic catgut sutures. The pleural cavity was drained. A gastrostomy was performed through a separate abdominal incision. The patient was much improved following this surgery. On the third postoperative day a well-drained esophagocutaneous

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fistula developed. The lung remained expanded. At discharge, the patient still had a small esophagopleurocutaneous fistula but was otherwise well and tolerating oral feedings.



FIG. 1. (Case 1) Barium swallow showing right pleural effusion and extravasation of barium.

#### CASE NO. 2

A 67 year old white man was seen in the emergency room on 1/10/65, one hour after the onset of back pain associated with vomiting. The patient was a habitual drinker. His chief complaint was that of acute distress due to difficulty in breathing and also to severe back pain which radiated to both shoulders. The patient preferred to sit up during physical examination. He was diaphoretic, with blood pressure of 180/80 and a pulse rate of 100. Sub-

cutaneous emphysema was present in the right supraclavicular region. The white blood cell count was 17,000. Chest x-rays showed a non-specific retrocardiac density. No identification of mediastinal emphysema was made. Barium swallow showed supradiaphragmatic extravasation on the left side. Six hours after the onset of symptoms a left thoracotomy and closure of the perforation in two layers was done. The patient developed delirium tremens and pulmonary complications immediately after surgery. An esophageal fistula with mediastinal abscess was drained through a posterior mediastinotomy approach on the tenth postoperative day. A feeding duodenostomy was also performed. The esophageal fistula closed spontaneously within 2 months. The patient was discharged 75 days after admission.

#### CASE NO. 3

A 54 year old white man reported to the emergency room on 12/14/64 because of persistent vomiting and vague substernal distress of 24 hours duration. The patient was a habitual drinker. While he was being examined, he complained of severe chest pain and vomited frank blood. He became diaphoretic and cyanotic, with blood pressure of 100/80 and pulse rate of 126. Chest x-ray was negative and white blood cell count was 7,000 with a hematocrit of 77%. By the time he reached the ward the patient was in severe respiratory difficulty and had a blood pressure of 60/0. A repeat chest x-ray showed hydropneumothorax on the left side. There was considerable tension and mediastinal shift. An intercostal tube was inserted with expansion of the lung and drainage of 1000 cc of blood. Despite replacement of blood loss and expansion of the lung, the blood pressure remained below 60 systolic and the pulse rate at 140. Barium swallow on two occasions at 3 hour intervals showed no abnormality. Examination of the pleural blood showed a pH of 5.0. The patient was taken to the operating room with a blood pressure of 50/0. The tentative diagnosis was that of ruptured esophagus. The only support for this diagnosis was the finding of a low pH in the pleural blood and the concomitant hematemesis and intrapleural hemorrhage. Following induction of anesthesia the pulse and blood pressure were not obtainable. Supportive therapy did not restore the blood pressure and the decision was made to operate despite the presence of shock. A left thoracotomy was performed and a 1½ inch laceration of the esophagus and overlaying pleura was found. About 300 cc of bloody fluid was present in the pleural space. A careful search was made for additional rents in the mucosa of the gastroesophageal junction but none were found. The laceration was closed in two layers using interrupted silk sutures. The patient showed marked and rapid improvement following evacuation of the pleura and opening of the mediastinum. By the time the chest wall was being closed the blood pressure was over 100 systolic and the pulse rate was 110. A gastrostomy was done. The patient had an uneventful postoperative course. He was placed on oral feedings by the sixth postoperative day and was discharged on the 20th postoperative day. No fistula nor abscess developed.

## CASE NO. 4

This 32 year old Negro man was seen in the emergency room on 4/20/65. The patient was intoxicated, had generalized body tremors, was very apprehensive, incoherent and complained of severe substernal pain. The patient was



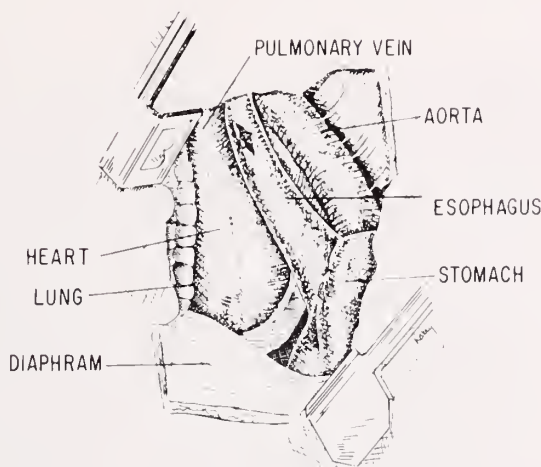
FIG. 2. (Case 4) Chest film showing minimal mediastinal emphysema, i.e., faint outlining of both right and left visceral mediastinal pleurae.

an inveterate alcoholic. No clear-cut history of vomiting could be obtained. When first seen, he had blood pressure of 140/70, pulse rate of 78, white blood cell count of 20,000 and serum amylase of 93 Somogyi units. Chest X-ray was reported as normal, although in retrospect early evidence of mediastinal emphysema was present (Fig. 2).

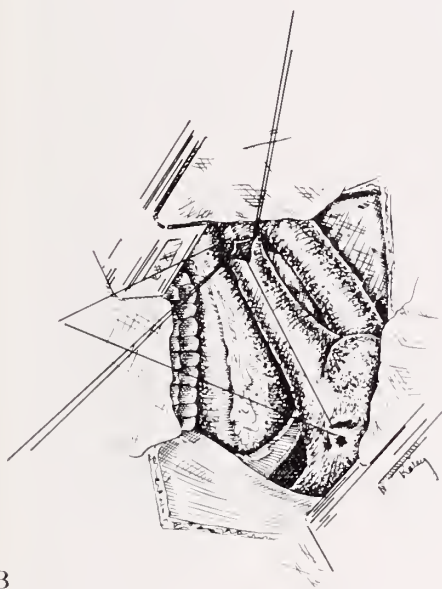
The patient was admitted for observation but within the next 6 hours his general condition deteriorated. He had, at this time, a temperature of 103°F.,



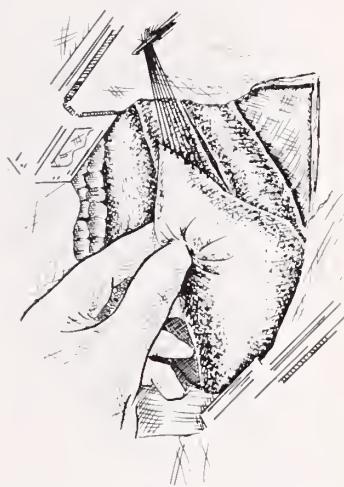
blood pressure of 100/80 and pulse rate of 140. Supraclavicular subcutaneous emphysema was now evident and chest X-ray revealed extensive air dissection of the mediastinum. The patient was then immediately explored through a left



A



B



C

FIG. 3. (Case 4) Schema indicating technique of utilizing fundal patch to reinforce mediastinal repair.

thoracotomy, with a tentative diagnosis of esophageal perforation. This was approximately 10 hours after admission. Barium swallow was not attempted. Exploration revealed that the mediastinal pleura was not ruptured but an esophageal tear was present in the usual place, just above the diaphragm.

The entire mediastinum was extensively dissected by air and a large amount of thin, greyish fluid with putrid odor was noted. At the site of rupture and along the edges of the separation, the wall of the esophagus was necrotic. The remainder of the esophageal wall was edematous and acutely inflamed. A single layer closure was done with loosely tied silk. The cardia was next herniated through the esophageal hiatus and the intact gastric wall was sutured around the esophageal tear as an external patch (Fig. 3). A radial counter incision, which had been made in the diaphragm to facilitate herniation of the stomach, was now closed with silk sutures. A gastrostomy was done through a separate incision. At the end of the procedure the pulse rate was 110 and of good quality. The blood pressure was 120/80. Postoperatively the patient developed delirium tremens and a right pleural effusion which required aspiration. The patient was placed on oral feedings on the sixth postoperative day. Barium swallow performed after operation showed no distortion and no evidence of hiatus hernia (Fig. 4). The patient was discharged 20 days postoperatively in excellent condition.

#### DISCUSSION

During the act of vomiting gastric contents are suddenly and forcibly released into the esophagus. The esophageal wall ruptures when the intraluminal pressure exceeds its bursting pressure, estimated to be 3.5–4.0 pounds per square inch. Heavy alcohol intake, esophagitis and proximal obstruction or spasm of the esophagus are predisposing factors. In the majority of cases, a longitudinal tear is found on the left side in the lower third of the esophagus. A fulminating mediastinitis, at first chemical and then bacterial, occurs, followed by a pleuritis. Spontaneous perforation of the esophagus results in a mortality, if untreated, of 25 per cent in the first 12 hours and 70 per cent by 24 hours.

A history of heavy alcohol intake, with vomiting followed by sudden substernal and epigastric pain, is typical and suggests the diagnosis. Diagnostic findings are mediastinal and subcutaneous emphysema, hydropneumothorax and extravasation of orally administered contrast media. Important as these clues are, they may be absent or may appear late in the course of the disease.

On admission, only one of our cases had clearly demonstrable mediastinal and subcutaneous emphysema. In another patient mediastinal emphysema was present but was so minimal that it was missed in the preliminary reading of the chest x-ray. Hydropneumothorax was absent in all 4 cases on the admission x-ray films. In one patient it appeared within 2 hours and in another patient it was demonstrated 3 days later. Neither of these two patients, however, showed evidence of mediastinal emphysema which was the dominant finding in the two cases with intact pleura. An esophagogram with demonstration of extravasation is the only confirmatory diagnostic test. Extraesophageal extravasation was present in two of our patients. In another patient esophagography, though repeated twice within 3 hours, was negative. At surgery the esophageal tear was occluded by fibrin clot. In the fourth case an

esophagogram was not done. In those patients with perforation of the pleura, pleural aspiration might reveal ingested dyes or foodstuff. A low pH indicates contamination by gastric juice. In one of our patients the pleural fluid had an amylase activity of 750 Somogyi units. His abdominal findings were so prom-



FIG. 4. (Case 4) Postoperative barium swallow showing neither distortion of the terminal esophagus nor hiatus hernia despite use of a fundal patch in the esophageal closure.

inent that an exploratory laparotomy was done on the day of admission with negative findings.

A high amylase activity of the pleural fluid has been previously reported in a case which, at postmortem, showed no disease of the pancreas but rather a perforation of the esophagus. However, hemorrhagic pancreatitis in a patient with Mallory-Weiss syndrome has also been described. Spontaneous

perforation of the esophagus and acute pancreatitis share the common background of heavy alcohol intake. In borderline cases the clinical picture may be very similar. In the differential diagnosis it is important to remember that both may be present at the same time.

Chest x-rays showed some degree of abnormality in all four patients. While not always diagnostic, these findings are present early and should alert to the possibility of intrathoracic disease. A non-specific retrocardiac density was described in three of our patients. It is desirable to verify the diagnosis before subjecting these very sick patients to major surgery but this is not always possible.

Occasionally the diagnosis is strongly suspected only by exclusion and only after the development of clinical manifestations. Absence of pneumomediastinum or failure to demonstrate extravasation of contrast media are considered by some to be sufficient grounds to withhold operation and wait for the appearance of positive diagnostic criteria. One of our patients, however, was explored without delay in the absence of definite evidence for perforation. There is some doubt that he would have survived for the time necessary to establish the diagnosis preoperatively. Considering the high early mortality of untreated cases, it would appear to us that, when there is strong suspicion but no proof, surgery is perhaps more justifiable than observation. In all cases a thoracotomy was done regardless of the elapsed time. All these patients were in poor condition and poor anesthetic risks. One was actually without measurable blood pressure or palpable pulse at the time of thoracotomy. In this patient an immediate and dramatic improvement followed evacuation of pleural and mediastinal fluid. In another patient explored three days after perforation, although his cardiovascular status was more stable, marked improvement followed rapid decortication and evacuation of pleural contents consisting of ingested material and pus. As pointed out by others, gastric juice within the mediastinum and pleura tends to perpetuate a shock-like condition which does not respond to conventional treatment and can be corrected only by adequate drainage. For this reason, quite apart from the expectation of a successful esophageal closure and also because tube drainage is unreliable in the presence of fibrin clots, we think that a thoracotomy should be used in all cases. Moreover, surgery should not be postponed when indicated because of the extremely poor condition of the patient. Surgery seems to be tolerated much better than delay in drainage, a situation usually true for other perforated viscera.

Closure of the perforation was done in all cases. In one case esophageal fistula was present on the third postoperative day. This patient, operated on the third day after perforation, had a persistent small fistula at the time he left the hospital four months postoperatively. In another patient reperforation occurred on the sixth postoperative day which required posterior mediastinotomy. The fistula closed within two weeks. In a third patient, despite early surgery, there was such esophageal tissue damage that only a single layer incomplete closure could be made. A fundoplasty was used to reinforce

the closure line. This patient had an uneventful postoperative course. In spite of the fact that it is not always successful and sometimes impossible, closure is the stated aim of surgery. The technique of using an external patch of highly vascularized fundic gastric wall, as proposed recently, seems to offer a convenient alternative in those cases otherwise doomed to prolonged morbidity or eventual mortality from an esophageal fistula. In the fourth case a two-layer closure of the perforation healed well with an uneventful postoperative course.

#### SUMMARY

Four consecutive cases of successful closures of spontaneous esophageal perforation are presented. The symptomatology, diagnostic features, surgical management and complications are discussed. Prompt surgery, adequate drainage of the chest and mediastinum and mechanical closure of the perforation will reduce the high morbidity and mortality of this condition.



# **Pulmonary Eosinophilic Granuloma**

## **Aspects of Pulmonary Function**

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### INTRODUCTION

In 1953, Histiocytosis X was presented as a distinct entity, a relationship having been established between the features of Letterer-Siwe disease, Hand-Schuller-Christian disease and eosinophilic granuloma (1). Numerous reports attest to the fact that Histiocytosis X may be found in disseminated, focal, or combined forms. Since 1928, at least sixty-three cases of pulmonary eosinophilic granuloma have been reported in the English literature, either with pulmonary involvement by itself, or as part of the disseminated form (2-8). Various titles ascribed to the pulmonary involvement (2) include: 1) Pulmonary Eosinophilic Granuloma, 2) Eosinophilic Granuloma of the Lung, 3) Pulmonary Histiocytosis X, 4) Primary Pulmonary Histiocytosis X, and 5) Chronic disseminated Histiocytosis X with early extra-skeletal lesions (pulmonary) resembling eosinophilic granuloma.

Only a few of these cases have had serial studies of pulmonary function tests in an attempt to understand the progressive nature of the disease. The purpose of this paper is twofold: 1) to present two cases of pulmonary eosinophilic granuloma, with results of serial pulmonary function tests over a long period of time, and 2) to correlate previous data from the literature with these two cases in an attempt to link the pulmonary function tests with the pathologic process at the time of test performance.

### METHODS

Lung volume studies in 1961 and 1964 were performed on the two patients using a closed circuit spirometer. The functional residual capacity was determined by the closed circuit helium dilution method, and residual volume calculated by subtracting the expiratory reserve volume from the functional residual capacity. Ventilation was measured with the subject breathing room air and a mixture containing fourteen per cent oxygen and eighty-six per cent nitrogen. Simultaneous anaerobic collections were made of arterial blood and expired gases after the patient had achieved steady-state inspiration of the various gas mixtures.

Arterial blood and expired gases were analyzed as previously described (9), and the respiratory quotient, oxygen consumption and alveolar-arterial oxygen gradient were then calculated. Arterial oxygen and carbon dioxide were

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measured by direct electrode techniques using a meter designed for this. The measured oxygen saturation and the oxygen saturation calculated from the dissociation curve agreed in each sample.

Dynamic lung compliance was measured from several tidal volumes by a method of Mead. This technique and normal values have previously been reported from this laboratory (10).

#### CASE REPORTS

##### *Case No. 1*

A 30 year old white male teacher was admitted to the Bronx Veterans Administration Hospital for the second time in September, 1964, for reevaluation of eosinophilic granuloma involving bone and lung.

The diagnosis of eosinophilic granuloma of bone was first made in February, 1954, at age 19 in an Air Force hospital. A skeletal survey performed at that time because of bone pain revealed cystic areas in the left femur and right parietal region of the skull. Biopsy specimens substantiated the diagnosis and from September, 1954, to March, 1961, the patient received intermittent radio-therapy to these areas for recurrent pain.

In March, 1961, a routine chest film showed a "lacy appearance," the major symptoms at this time being anorexia, weight loss, and cough. The only other pulmonary complaint ever noted was in August, 1954, when the patient experienced left pleuritic chest pain which subsided spontaneously. A left open lung biopsy in September, 1961, revealed eosinophilic granuloma (Fig. 1). Bronchoscopy and a scalene node biopsy were not remarkable.

In October, 1961, the patient was transferred to the Bronx Veterans Administration Hospital for pulmonary evaluation. A chest film showed "fine interstitial markings" throughout both lung fields; pulmonary function studies are shown in Table I. A slight reduction in lung volumes along with venous admixture and diffusion impairment were demonstrated. The patient was treated with bronchodilators and antibiotics with clinical improvement.

From 1961 until August, 1964, the patient's chest film changed from a lacy appearance to a diffuse reticular-nodular infiltrate with honey-combing (Fig. 2). In August, 1963, lung volumes were still slightly reduced. In August, 1964, the patient developed a new lytic lesion in the right femur and pulmonary function studies (Table I) now revealed an increase in residual volume, arterial unsaturation at rest and the same level of venous admixture and diffusion impairment. The chest film at this time showed the "honeycomb" appearance. The patient was discharged in October, 1964, without further treatment.

Coincident with this patient's disease process, a diagnosis of paranoid schizophrenia was made in January, 1962. He apparently had shown signs of mental instability in 1953, 1956-1961, and 1962-1964, without evidence of diabetes insipidus.

*Comment:* This patient has had proven disseminated eosinophilic granu-

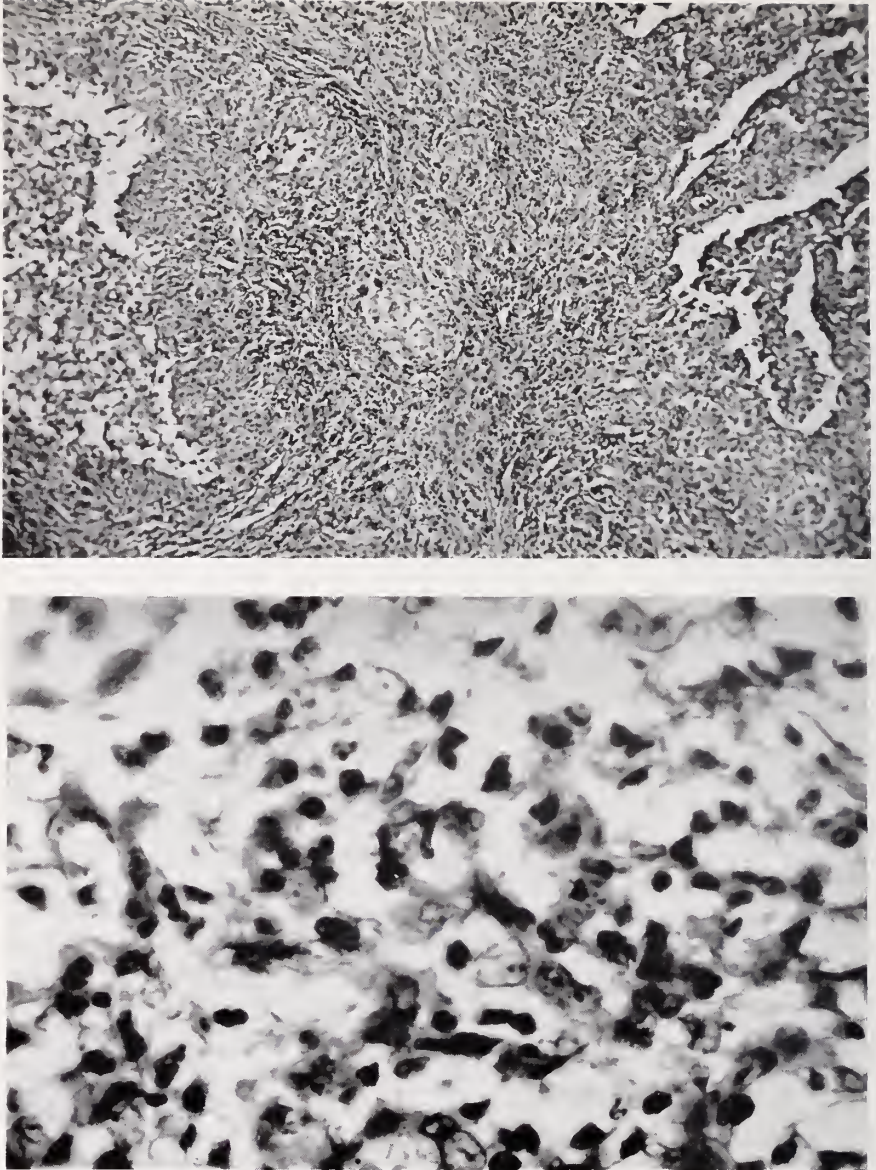


FIG. 1. Lung biopsy, K. C., September, 1961, showing a granuloma containing eosinophils and histiocytes.

loma, with bone involvement for almost eleven years, and pulmonary involvement for four or more years. Serial pulmonary function studies demonstrated an increase in residual volume, development of venous admixture, and some impairment of diffusion. The last reported studies were associated with "honeycomb" emphysema.

## Case No. 2 (11)

M. R., a 33 year old Puerto Rican male chauffeur, was readmitted to the Bronx Veterans Administration Hospital in June, 1964, with the chief complaint of nervousness.

TABLE I  
*Pulmonary Function Studies in Pulmonary Eosinophilic Granuloma*

	VC	RV	RV/ TC	MVV	LC	SaO <sub>2</sub>	PaO <sub>2</sub>	PaCO <sub>2</sub>	A-a gradient	A-a (LO) gradient
	( )% pred.		30%	( )% pred.	0.19± 0.03L/cm H <sub>2</sub> O	96 ± 2%	90 or > mm Hg	40 ± 2 mm Hg	<15	<15
K.C.										
10/19/61	4670 (85%)	930	16%	93 (66%)		96%	RA 70 LO 38	RA 35 LO 33	34	24
8/23/63	4700 (85%)	1045	19%							
9/23/64	4640 (84%)	2535	32%	115 (88%)		92%	RA 76 LO 43	RA 36 LO 34	34	18
M.R.										
2/17/54	3850 (83%)			95.2 (65%)						
7/14/55	3931 (86%)	1516	27%	147 (105%)		96%				normal
6/25/57	4592 (100%)									
7/6/60	4592 (100%)			147 (105%)						
8/10/64	4340 (95%)	2320	35%	107 (78%)	0.17	96%	RA 57 LO 43	RA 32 LO 29	48	21

VC = vital capacity

RV = residual volume

TC = total capacity

MVV = maximal voluntary ventilation

LC = lung compliance

SaO<sub>2</sub> = arterial saturation

PaO<sub>2</sub> = arterial O<sub>2</sub> tension

PaCO<sub>2</sub> = arterial CO<sub>2</sub> tension

RA = room air

LO = low oxygen (14%)

At age 23 in March, 1954, the patient had the diagnosis of pulmonary eosinophilic granuloma made by a right open lung biopsy in Puerto Rico. His symptoms had begun in March, 1951, and consisted of chills, fever, cough and mild chest pain. Chest films had shown a diffuse, fine infiltrate bilaterally in the lung fields. Pulmonary studies in 1954 are shown in Table I and demonstrate a slight decrease in lung volume at the time of the lung biopsy.

From June, 1955, to November, 1960, the patient had numerous hospital



and clinic admissions to the New York Veterans Administration Hospital for increased dyspnea. Pulmonary function studies in 1955, 1957, and 1960 now showed normal lung volumes along with normal arterial saturation and no diffusion impairment. Chest films over this period showed no change, bone films remained normal and the complete blood count showed a persistent elevation of hemoglobin and hematocrit.

A repeat chest film in January, 1961, showed a reticular-nodular infiltrate, but the patient's clinical state remained stable from 1961 to June, 1964. A



FIG. 2. Chest film, K. C., August, 1964, showing bilateral "honeycomb" emphysema.

chest film in August, 1964, at the Bronx Veterans Administration Hospital, showed "honeycomb" emphysema (Fig. 3) and pulmonary function tests now showed an increase in residual volume, slight reduction in maximum voluntary ventilation, venous admixture, and impairment of diffusion. There was no change in the bone films and all other organ evaluation was not remarkable. No specific treatment was given at this time.

It is of interest that this patient also had a diagnosis of schizophrenia made during the course of his disease process. He experienced periods of mental instability in 1955-1960, 1961, and 1964 without evidence of diabetes insipidus.



*Comment:* This patient has had proven pulmonary eosinophilic granuloma for about fourteen years without any other organ involvement, and has shown a slow development of "honeycomb" emphysema. He has received no definitive treatment and pulmonary function studies have shown an increase in residual volume, reduced maximum voluntary ventilation, venous admixture and some impairment of diffusion.



FIG. 3. Chest film, M. R., August, 1964, showing bilateral "honeycomb" emphysema.

#### DISCUSSION

Both cases exemplify the protracted course which the benign form of pulmonary eosinophilic granuloma may follow. Recent reports have shown that pulmonary eosinophilic granuloma may remain fairly stable even after fifteen years (4). Reviews by Thannhauser (12), Farber (13), Lichtenstein (1), and Van Creveld (14), have brought about an understanding of the trivalent nature of Histiocytosis X, and pathological studies by Rowland (15), Heppelstone (16), Auld (17), and Gough (18), have shown that there may be five major phases of histologic progression in pulmonary eosinophilic granuloma. These include: 1) a proliferative phase in which there is proliferation of reticulo-histiocytic elements, 2) a granulomatous phase with focal formation of giant cells, fibrils, eosinophils, and an increase in the number of blood vessels, 3) a "hypersensitive" phase which includes perivascular infiltration of

round cells, peribronchiole infiltration of round cells, eosinophils in arteriolar walls, and peripheral eosinophilia, 4) an xanthomatous phase with the presence of foam cells, and 5) a fibrotic phase, the so-called healing phase.

The term "honeycomb" lungs, first presented in 1949 (19), has been used to describe a stage of pulmonary eosinophilic granuloma, both radiologically and histologically. The pathogenesis of "honeycomb" lungs, and its relation to pulmonary eosinophilic granuloma has been discussed previously (8, 19, 20, 21). Utilizing this information plus the above mentioned pathologic data, it is possible to postulate the mechanism of production of the pulmonary function abnormalities.

Reduction in lung volumes may occur in the first stage of pulmonary eosinophilic granuloma. This was demonstrated in both cases and coincides with other case studies in which it was found that the early diffuse proliferative infiltration may encroach on the air spaces and cause diminished lung volumes (3). Furthermore, this phase may also be associated with a decreased dynamic lung compliance, an abnormality previously shown (22) but not demonstrated in the two cases. The lung volumes may subsequently improve, as shown in Case No. 2, usually as a result of receding infiltration (3). Then, as the pathologic process advances, with granuloma formation and expectoration (20), bronchiolar obstruction due to secretions and endobronchial disease (19), or fibrosis (8, 18, 19), the "honeycomb" or cystic phase results. At this time there is an increase in functional residual capacity and residual volume, again shown in both cases presented in this report. This increase in residual volume has been noted previously in other cases (2, 3), but had been attributed only to a general state of lung distension. Because of bronchial obstruction during this stage, the maximum voluntary ventilation may be affected (3), but a reduced value in this test may also be due to the weakened state of the patient as demonstrated in both cases. Venous admixture usually results in pulmonary eosinophilic granuloma, hypoxemia being a consistent finding in the two patients and in previous case studies (2). This is a consequence of an alteration of the ventilation-perfusion ratio which seems to exist at any stage of the disease process.

Diffusion impairment in pulmonary eosinophilic granuloma may exist as a consequence of 1) fibrosis causing thickening of the "alveolar-capillary membrane" (3, 23), 2) diminished total surface area as a result of dilated air spaces (24), or 3) reduction in size of the pulmonary vascular bed as a result of the hypersensitivity reaction or fibrosis (3, 17). In the two presented cases, a cause and effect relationship as to which of the factors was the most essential in producing this abnormality cannot be established. However, it was noted that in Case No. 2 diffusion impairment did not occur until the "honeycomb" phase appeared. Thus, following the statement that the "clinical manifestations of eosinophilic granuloma depend on the site of the disease process" (25), similarly it seems that the pulmonary function tests in pulmonary eosinophilic granuloma depend on the existing pathologic state.

It is of interest that both patients developed schizophrenia during the course

of their disease. Since the etiology of schizophrenia is not known, no further discussion of this relationship can be undertaken at this time.

#### SUMMARY

Two cases of pulmonary eosinophilic granuloma are reported, one with disseminated eosinophilic granuloma of bone and lung; the other with pulmonary involvement alone. Both cases had serial pulmonary function tests over a period of years the last studied stage of each being similar in that each showed "honeycomb" emphysema.

Pulmonary function abnormalities correlate well with the clinical-pathologic status of this disease. The increase in residual volume, venous admixture and diffusion impairment in the two presented cases, when combined with previous case studies, demonstrate this correlation.

#### REFERENCES

1. Lichtenstein, L.: Histiocytosis X: Integration of Eosinophilic Granuloma of Bone, "Letterer-Siwe Disease," and "Schuller-Christian Disease" as Related Manifestations of a Single Nosologic Entity. *Arch. Path.*, 56: 84, 1953.
2. Williams, A. W., Dunnington, W. G., and Berte, S. J.: Pulmonary Eosinophilic Granuloma: A Clinical and Pathologic Discussion. *Ann. Int. Med.*, 54: 30, 1961.
3. Hoffman, L., Cohn, J. E., and Gaensler, E. A.: Respiratory Abnormalities in Eosinophilic Granuloma of the Lung. *New England J. Med.*, 167: 577, 1962.
4. Bickers, J. N., Buechner, H. A., and Ekman, P. J.: Eosinophilic Granuloma: Its Natural History and Prognosis. *Am. Rev. Resp. Dis.*, 85: 211, 1962.
5. Roland, A. S., Merdinger, W. F., and Froeb, H. F.: Recurrent Spontaneous Pneumothorax: A Clue to the Diagnosis of Histiocytosis X. *New England J. Med.*, 270: 73, 1964.
6. Hicks, B. J., Bullock, A. C., and Granville, G. E.: Pulmonary Eosinophilic Granuloma with Diabetes Insipidus. *Dis. Chest*, 43: 208, 1963.
7. Duckler, L.: Pulmonary Eosinophilic Granuloma: Report of a Case. *Dis. Chest*, 44: 205, 1963.
8. Thompson, J. R., and Langer, S.: Eosinophilic Granuloma of the Lungs. *Dis. Chest*, 46: 533, 1964.
9. Stone, D. J., Schwartz, A., Feltman, J. A., and Lovelock, F. J.: Pulmonary Function in Sarcoidosis. *Amer. J. Med.*, 15: 468, 1953.
10. Stone, J. D., and Keltz, H.: The Effect of Respiratory Muscle Dysfunction on Pulmonary Function. *Am. Rev. Resp. Dis.*, 88: 621, 1963.
11. Laios, N. C., and Lovelock, F. J.: Eosinophilic Granuloma of the Lung. *Am. Rev. Resp. Dis.*, 83: 394, 1961.
12. Thannhauser, S. J.: *Lipidoses: Diseases of the Intracellular Lipid Metabolism*. New York: Grune & Stratton, Inc., 1958.
13. Farber, S.: The Nature of Some Diseases Ascribed to Disorders of Lipid Metabolism. *Am. J. Dis. Children*, 68: 350, 1944.
14. Van Creveld, S.: The Lipidoses. *Advances in Pediatrics*, 6: 190, 1953.
15. Rowland, R. S.: Xanthomatosis and the Reticulo-Endothelial System. *Arch. Int. Med.*, 42: 611, 1928.
16. Heppelstone, A. G.: The Pathology of Honeycomb Lung. *Thorax*, 11: 77, 1956.
17. Auld, D., Major(MC)USAF: Pathology of Eosinophilic Granuloma of the Lung. *Arch. Path.*, 63: 113, 1957.

18. Gough, J.: Pathological Changes in the Lungs Related to Cor Pulmonale. Conference on Cor Pulmonale, New York Heart Association, January, 1965.
19. Oswald, N., and Parkinson, T.: Honeycomb Lungs. *Quart. J. Med.*, 18: 1, 1949.
20. McNeill, R. S., and Cameron, H. M.: Hand-Schuller-Christian Disease: Report of a Case with Unusual Lung Changes. *Thorax*, 10: 314, 1955.
21. Schaffner, F.: Clinico-Pathological Conference. *J. Mt. Sinai Hosp.*, 31: 138, 1964.
22. Macklem, P. T., and Becklake, M. R.: The Relationship Between the Mechanical and Diffusing Properties of the Lung in Health and Disease. *Am. Rev. Resp. Dis.*, 87: 47, 1963.
23. Renzetti, A., Eastman, G., and Auchincloss, II.: Chronic Disseminated Histiocytosis X With Pulmonary Involvement and Impairment of Alveolar-Capillary Diffusion. *Am. J. Med.*, 22: S34, 1957.
24. Comroe, J. H., Forster, R. E. II, Dubois, A. B., Briscoe, W. A., and Carlson, E.: *The Lung*. Chicago: Year Book Medical Publishers, Inc., 1963.
25. Livingston, H. J.: Eosinophilic Granuloma of the Lung. *New England J. Med.*, 259: 959, 1958.

# Massive Parasagittal Epidural Hematoma of Venous Origin

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Parasagittal epidural hematomas resulting from injury to the superior sagittal sinus are infrequent compared to the well-known extradural clot of middle meningeal artery origin. Although Hooper (1) noted that a clot occurred in the parasagittal region five times in 28 of his cases of epidural hematomas, the incidence has been much lower in other series, varying from 2% to 9% (2-6). Additional authors have reported cases in which the superior sagittal sinus was the source of epidural hemorrhage (7-12). The increasingly widespread utilization of angiography in head injuries has resulted in the more frequent preoperative diagnosis of this condition and has contributed significantly to its management.

The following case illustrates the clinical and radiological features of this condition and demonstrates the massive size which the lesion may attain and still be remedial by surgical intervention.

## CASE REPORT

A 32-year old semicomatose woman was brought to Mount Sinai Hospital, City Hospital at Elmhurst Division, in 1964. She had been well until she was assaulted several hours prior to arrival at the hospital. There were no immediate ill effects from her injuries, but her level of consciousness suddenly deteriorated and she developed right-sided focal seizures.

On examination there were multiple contusions and abrasions over the face and body. The blood pressure was normal but the pulse was rapid and irregular. A large boggy subgaleal hematoma could be palpated in the region of the vertex of the skull. The patient was semicomatose. She did not speak or follow commands despite attempts to arouse her. The cranial nerves were normal except for early bilateral papilledema. There was a flaccid paralysis of the right upper extremity. The right lower extremity was paretic. Muscle tone was increased in both lower extremities, which tended to be maintained in a position of extension at the hips and knees. The deep tendon reflexes were absent in the right upper extremity and hyperactive in both lower extremities. Plantar responses were extensor bilaterally. The patient withdrew all extremities, except the right upper extremity, to painful stimulation.

Laboratory studies were normal. Skull x-rays demonstrated a transverse linear fracture at the vertex. The fracture line crossed the sagittal suture.

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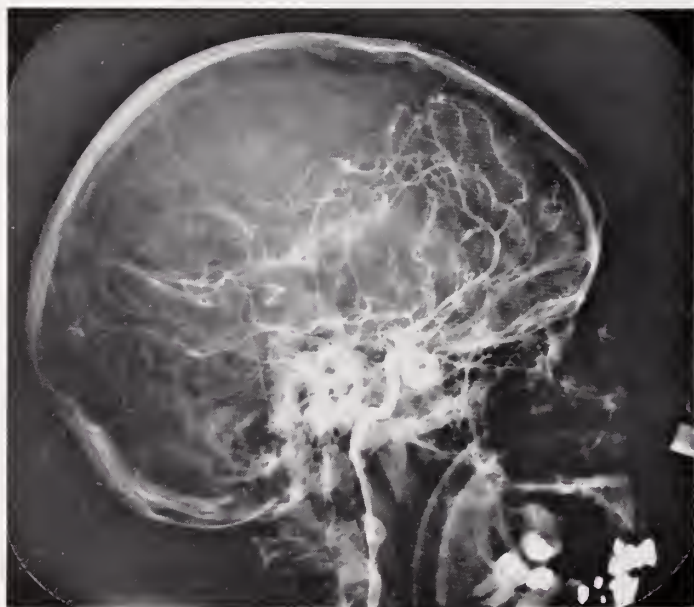


FIG. 1A and 1B. Arterial phase demonstrating large avascular mass in parasagittal region. Shift of anterior cerebral artery toward the right side.

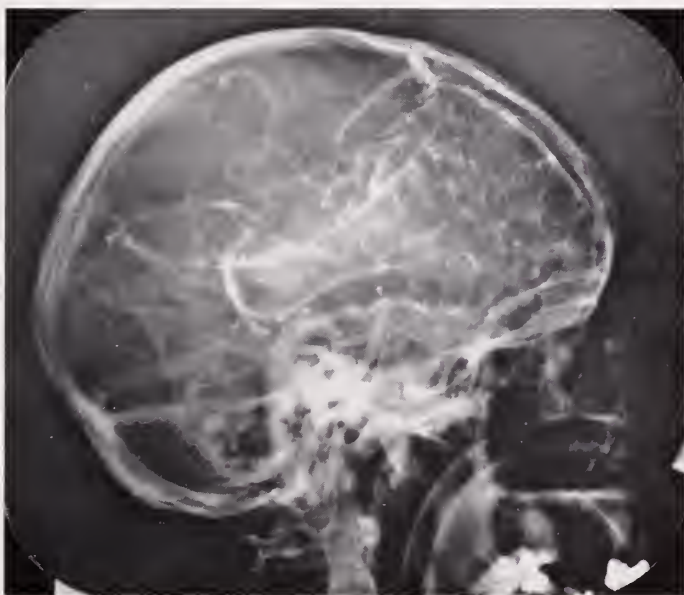


FIG. 2A and 2B. Venous phase. Marked inferior displacement of the superior sagittal sinus from the inner table of the skull.

Lumbar puncture revealed grossly bloody cerebrospinal fluid with a pressure of 360 mm.

A left carotid arteriogram was carried out. Only the arterial phase was seen after six serial x-rays at one-second intervals. The arterial phase (Figs. 1A, 1B) demonstrated marked downward displacement of the anterior cerebral artery from the vertex of the skull by an avascular bilateral parasagittal posterior frontal-parietal mass. The anterior cerebral artery was shifted toward the right side. Timing between serial films was increased to three-second intervals. The venous phase (Figs. 2A, 2B) was demonstrated 12 seconds after the dye entered the carotid siphon. The superior sagittal sinus was inferiorly displaced 7 cm from the inner table of the skull.

The patient continued to deteriorate and became decerebrate with a fixed dilated left pupil.

A craniotomy was performed. A large biparietal bone flap was turned. Two linear skull fractures, which crossed the sagittal suture, were included in the bone flap. A huge extradural hematoma, consisting of several hundred c.c.'s of clotted blood, markedly depressed the superior sagittal sinus. The hematoma was evacuated. Several bleeding points, which arose from the sagittal sinus, were easily controlled by gelfoam. The dura was opened but no subdural hematoma was found.

The patient made an uneventful recovery. Six weeks after surgery the neurological examination was negative and the patient was discharged from the hospital.

#### DISCUSSION

Although injury to the superior sagittal sinus due to depressed fractures or penetrating wounds of the skull is not rare (12-14), extradural hematomas of dural sinus origin are infrequent. Because of the low venous pressure of the sagittal sinus, an extradural clot usually does not form even though the sinus is torn (2). Thus, the common forms of injury to the dural sinus are not often associated with epidural hematoma.

The clinical picture closely resembles that of an extradural hematoma of middle meningeal artery origin. The course may be acute, subacute or chronic (11). A lucid interval of variable duration will be present. Signs of increasing intracranial pressure and possibly focal neurological deficits commonly develop. Associated damage to other intracranial structures may result in marked variations in the clinical picture. A subcutaneous scalp hematoma, which results from blood leaking through the overlying skull fracture into the scalp tissue, is often present.

Plain skull films almost invariably demonstrate a diastasis of the sagittal suture or a linear or depressed fracture in the region of the vertex. Carotid arteriography is of great value in determining the size and location of the clot and the presence of associated intracerebral involvement. Displacement of the superior sagittal sinus from the inner table of the skull, originally described by Wickbom (15) and subsequently illustrated by other authors (7,

8, 11, 16-19), distinguishes an epidural from a subdural hematoma. Alexander (7) suggested that compression of the lacunae, into which the rolandic veins drain superiorly, may compromise the venous drainage and be a factor in the rise of intracranial pressure and slowing of the cerebral circulation. In the present case, the circulation time was 12 seconds. Circulation time, defined by Greitz (20) as the time required for the maximum concentration of contrast substance in the carotid siphon to reach the maximum concentration in parietal veins, greater than 6 seconds is considered to be definitely prolonged.

Utilizing the accurate localization of the clot by angiography, an adequate well-placed bone flap may be turned and the hematoma evacuated under direct vision. The bone flap should be made across the sagittal suture corresponding to the area of the hematoma so that direct visualization of the superior sagittal sinus is possible. Active bleeding from the sinus usually may be controlled with gelfoam or muscle but at times sutures may be required to repair tears in the sinus. Attempt at removal of the hematoma by multiple burr holes may not be adequate and several authors (6, 7, 10) have experienced reaccumulation of the clot following attempt at burr hole aspiration. With an adequate bone flap the clot can be more completely evacuated and the bleeding better controlled, thereby decreasing the danger of recurrence. The dura should be opened to see if there is an associated subdural hematoma. In certain instances in which the clot is thin and the neurological deficit is not severe, conservative management may be attempted in the hope that the clot will resorb spontaneously (7, 9, 21).

#### SUMMARY

A patient with a massive epidural hematoma of superior sagittal sinus origin has been presented. The characteristic clinical and radiological features have been discussed.

#### REFERENCES

1. Hooper, R. (S.): Observations on Extradural Haemorrhage. *Brit. J. Surg.*, 47: 71, 1959.
2. Gurdjian, E. S., and Webster, J. E.: Extradural Hemorrhage. A Collective Review of the Literature and a Report of 30 Cases of Middle Meningeal Hemorrhage and 4 Cases of Dural Sinus Hemorrhage Treated Surgically. *Internat. Abstr. Surg.*, 75: 206, 1942.
3. LeCount, E. R., and Apfelbach, C. W.: Pathologic Anatomy of Traumatic Fractures of Cranial Bones and Concomitant Brain Injuries. *J. A. M. A.*, 74: 501, 1920.
4. McKissock, W., Taylor, J. C., Bloom, W. H., and Till, K.: Extradural Haematoma. Observations on 125 Cases. *Lancet*, 2: 167, 1960.
5. Munro, D., and Maltby, G. L.: Extradural Hemorrhage. A Study of 44 Cases. *Ann. Surg.*, 113: 192, 1941.
6. Raaf, J.: Massive Extradural Hematoma. *Am. J. Surg.*, 76: 567, 1948.
7. Alexander, G. L.: Extradural Haematoma at the Vertex. *J. Neurol. Neurosurg. & Psychiat.*, 24: 381, 1961.
8. Iwata, K.: Sagittal Sinus Hematoma. Angiographic Demonstration and Clinical Pathology. *Pac. Med. Surg.*, 76: 340, 1964.
9. Lindgren, S. O.: Acute Severe Head Injuries. Clinical Diagnosis and Classification



- with Respect to Early Prognosis and Treatment. *Acta chir. Scandinav.*, Suppl. 254, 49 pp., 1960.
10. Reichert, F. L., and Morrissey, E. J.: Extradural Venous Hemorrhage. *Ann. Surg.*, 113: 204, 1941.
  11. Stevenson, G. C., Brown, H. A., and Hoyt, W. F.: Chronic Venous Epidural Hematoma at Vertex. *J. Neurosurg.*, 21: 887, 1964.
  12. Wharton, H. R.: Wounds of the Venous Sinuses of the Brain. An Analysis of Seventy Cases. *Ann. Surg.*, 34: 81, 1901.
  13. Gross, S. W., and Ehrlich, W.: *Diagnosis and Treatment of Head Injuries*. New York: Hoeber, 1940, p. 99.
  14. Holmes, G., and Sargent, P.: Injuries of the Superior Longitudinal Sinus. *Brit. Med. J.*, 2: 493, 1915.
  15. Wickbom, I.: Angiography by Post-Traumatic Intracranial Haemorrhages. *Acta radiol.*, 32: 249, 1959.
  16. Campiche, R.: Hématome Épidural Subaigu de Localisation Inhabituelle avec son Image Artériographique. *Radiol. Clin.*, 31: 95, 1962.
  17. Lindgren, E.: Röntgenologie. In *Handbuch der Neurochirurgie*. Vol. 2. Ed. Olivecrona, H. and Tönnis, W. Springer-Verlag-Berlin, 1954, p. 223.
  18. Pecker, J., Javalet, A., and Le Menn, G.: L'Hématome Extra-Dural. Réflexions sur une Série de 111 Cas Personnels. *Neuro-Chirurgie*, 5: 428, 1959.
  19. Tiwisina, T. and Stäcker, A. D.: Die frischen Schädel-Hirnverletzungen im Gefäßbild. *Chirurg.*, 30: 344, 1959.
  20. Greitz, T.: A Radiologic Study of the Brain Circulation by Rapid Serial Angiography of the Carotid Artery. *Acta radiol.*, Suppl. 140, p. 123, 1956.
  21. Frykholm, R.: Discussion at the Meeting of the Scandinavian Neurosurgical Society at Lund on August 29th, 1950. Cited by Brodin, H.: Extradural Hematomas. *Acta chir. scandinav.*, 102: 99, 1952.



# Effects of Phenothiazine Discontinuation in Patients Compensated from Acute Psychosis

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Physicians have rapidly become accustomed to the extensive use of phenothiazine medication in the treatment of psychotic patients. It is difficult to realize that although these compounds were first studied in 1883 (1), their first therapeutic application came as late as 1943. The psychotropic usefulness of the phenothiazines was recognized only thirteen years ago by Delay, Deniker and Harl (2).

Since then many different compounds deriving from the phenothiazine nucleus have been studied; their clinical indications, dosages, side effects and contraindications have been well described. The usefulness of these compounds in the rapid control of acute psychotic symptomatology has been demonstrated (3). Their value in the adjustment and maintenance of chronic psychotic patients has been recognized (4, 5).

Some questions remain unresolved. The problem of how long to continue phenothiazine administration in chronic patients has not been clearly answered (6). Winkleman espouses the generally accepted opinion that at least several months of optimum dosage levels are indicated before reduction should be attempted (7). Rosati divided the treatment program of chronic schizophrenies into four phases during which he varied dosage and length of time of administration of phenothiazines but no significant difference in the rate of relapse was found between the four groups (8). Lehman concluded from his study that if there is any doubt in a case it is better to continue medication than to discontinue it and better to increase rather than decrease the maintenance dosage (9).

All of these studies have demonstrated that at least some chronic schizophrenic patients tend to relapse when medication is discontinued or reduced below a certain level. Forrest *et al.* have described clinical cases which have relapsed with discontinuation of medication and discussed the relative roles of the discontinuation as well as of the environmental, familial and occupational stresses. They have also noted the relation of relapse in the face of discontinuation of medication to a concomitant failure in the doctor-patient relationship (10).

## CASE REPORTS

There has been no report in the literature which describes the effect of discontinuation of phenothiazine therapy in patients who have experienced their first clinical acute psychotic decompensations.

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Two such cases were treated by one of the authors. A third was personally observed by both authors. Five more were culled from the case records of the Department of Psychiatry of The Mount Sinai Hospital. All cases were treated between 1963-65. Of the eight cases, five patients discontinued their own medication. In three cases the medication was discontinued by the physician. The reasons for interruption of phenothiazine medication will be presented in each case record. Each patient was receiving psychotherapy in addition to medication.

*Case 1.* M.W., a 15 year old single, female, high-school student, experienced anorexia, depression and withdrawal the day following her first sexual experience. In the course of the next two weeks she developed ideas of reference. She felt that television programs referred to her. She thought that she could make her dog talk to her. She claimed that she was pregnant.

Because of agitation and assaultiveness closed hospitalization was necessary. She was treated for thirty days with chlorpromazine 400 mg p.o. q.i.d. Upon release from isolation, following two weeks of hospitalization, her behavior remained bizarre and mischievous; she mixed all her food together, emptied other patients' belongings from their drawers, or compulsively pushed all buttons and switches available to her. Her verbal communications were unintelligible.

By the fourth week of her hospitalization she was able to communicate and socialize effectively. No further bizarre or agitated behavior was observed. She was then interviewed for admission to The Mount Sinai Hospital. At the interview she was not delusional. She remembered having had some unusual ideas which she was reluctant to discuss. Her affect was one of depression. The diagnosis was schizophrenic reaction, paranoid type, acute with depression. She remained stabilized in this condition for the following week.

At 9:00 p.m. on the night prior to transfer the patient received her usual dose of 400 mg of chlorpromazine p.o. Upon arrival at The Mount Sinai Hospital she appeared drowsy and had signs of Parkinsonism. No chlorpromazine was ordered until further evaluation could be completed. By 3:00 p.m., eighteen hours after the last dose of chlorpromazine, she had become agitated, bizarre and her speech was pressured and incoherent. Chlorpromazine 400 mg p.o. was ordered stat and q.i.d.

By the tenth day of hospitalization she was calm and coherent. She suffered from severe nasal congestion and edema with bacterial superinfection. Because of this and Parkinsonian signs the chlorpromazine dosage was gradually decreased and thioridazine 25 mg p.o. t.i.d. was substituted. She continued in a compensated state and was discharged to private therapy three weeks later.

*Case 2.* S.L., a 25 year old single, male, stock market analyst had been in individual psychotherapy for one year because of anxiety and nail biting. Because of failure to progress he was transferred to group psychotherapy. In the first session his homosexual tendencies were commented upon by the group, following which he became hypomanic and delusional. He felt as if he did not require sleep. He described himself as being in a "special psychic state"

wherein he could communicate by extrasensory perception. He impulsively lay down on the sidewalk and was taken forcibly to a city hospital.

In the two weeks he was there he received no medication. He developed the fixed delusion that he was the second Messiah. His diagnosis was schizophrenic reaction, acute, paranoid type. He was then transferred to a closed private hospital. There he was treated with chlorpromazine 100 mg p.o. q.i.d. for two weeks. He was then discharged home, well compensated and without further medication. He was readmitted to the private hospital two days later, agitated and delusional. Chlorpromazine 100 mg p.o. q.i.d. was reinstituted.

Within two to three days he became calm and was transferred to The Mount Sinai Hospital. His medication was continued. He remained delusional. During the next five days chlorpromazine was increased to 400 mg p.o. q.i.d. On this dosage he remained delusional and became drowsy. Eight days later trifluoperazine 2 mg p.o. b.i.d. was added. This drug was increased slowly as the chlorpromazine dosage was diminished, since antipsychotic effect without sedation was desired.

In two weeks' time the chlorpromazine was entirely discontinued. The patient was receiving trifluoperazine 5 mg p.o. q.i.d. He was awake and participating in ward activities. He was no longer actively delusional, but clung to the belief that he had been in a special psychic state. Three weeks later he was mobilized to the Night Hospital, from which he went to work daily for two weeks. He was then discharged to the clinic.

When again seen in the clinic, one week after discharge, he was agitated and delusional. He felt that he could communicate with God through his fingertip. He disclosed that he had discontinued all medication two days after discharge from the hospital, ostensibly because he could not find the time to take it while at work. Chlorpromazine 100 mg p.o. b.i.d. was reinstituted. The following week he was calmer and no longer delusional. He complained of drowsiness. He remained well compensated over the next six months and chlorpromazine was gradually discontinued.

One year later, on the anniversary of the first acute decompensation, he experienced a brief flurry of hypomania and hallucinosis. Chlorpromazine 100 mg p.o. h.s. was reinstituted for two weeks and the patient is now maintained on trifluoperazine 5 mg p.o. b.i.d.

*Case 3.* N.G., a 46 year old single, male salesman became depressed one year prior to admission. In the two months preceding admission he began to ruminate about his health, and also experienced anorexia and constipation. Two days prior to admission he became obsessed with the thought "kill, kill." The admission diagnosis was involutional psychosis. Because of agitation he was treated with chlorpromazine 100 mg p.o. q.i.d.

During the first three weeks of hospitalization the obsessive rumination ceased and he became less agitated. He remained in the hospital for three months. He was no longer depressed at the time of discharge. Chlorpromazine 100 mg p.o. q.i.d. was continued for one year in the Aftercare Clinic.

Shortly before the anniversary of his first admission and coincident with

the onset of an illness of his mother, with whom he had always lived, he failed to attend clinic. He also discontinued his medication as he felt that he was well. He was admitted to the hospital two weeks later, agitated, depressed and delusional; he believed that the hair on his chest was growing inward and would smother him. The diagnosis on this admission was schizophrenic reaction, paranoid type. He was treated with chlorpromazine 150 mg p.o. q.i.d.

Within forty-eight hours he was calmer and no longer delusional. He remained somewhat depressed. He worried about his mother's illness and the possible loss of his job due to hospitalization. He remained in the hospital six weeks. During this time his mother underwent surgery. Following her discharge, he was discharged and resumed working. He is being followed in the Aftercare Clinic and is taking chlorpromazine 150 mg p.o. q.i.d. He has had no further symptoms.

*Case 4.* C.A., a 19 year old married Puerto Rican mother was admitted to the Ophthalmology Service because she had had decreasing vision in the left eye for one month. On the day following admission she appeared to lose consciousness, rolled her head continuously from side to side and shouted for help. Similar episodes occurred three times within the next twenty-four hours. The psychiatric consultant found the patient expressing the wish to die. She was otherwise unresponsive. She was transferred to the Psychiatric Service where she remained unresponsive. She could not be fed per os. The diagnostic impression was schizophrenic reaction, catatonic type, acute.

On the following day, three days after admission to the hospital, the patient was treated with chlorpromazine 50 mg p.o. t.i.d. Within twenty-four hours she became responsive. She ate and socialized. After five days of clinical remission, chlorpromazine was discontinued. The physician did this in the belief that the patient was stabilized. Twenty-four hours later the patient had another episode of head rolling and screaming. This episode was aborted in an hour by 100 mg chlorpromazine p.o. followed in twenty minutes by chlorpromazine 100 mg i.m. Chlorpromazine 50 mg p.o. t.i.d. was reinstituted.

The episodes continued once to twice a day over the next nine-day period. The chlorpromazine was increased to 100 mg p.o. q.i.d. Four days later the patient experienced her last episode, this one consisting only in the feeling that she might faint. She remained in the hospital an additional three weeks. Then believing herself well, she signed out against medical advice without medication. She reappeared two days later in an agitated state. She then accepted the suggestion of a voluntary admission to a state hospital.

*Case 5.* M.W., a 25 year old, married, male market research assistant was well until two weeks prior to his admission. At that time, he was temporarily left in charge of the business. He became very anxious, felt impelled to work unusually hard until he had actually been working without sleep for four days. On the day of admission he began working on a mathematical equation which resulted in the proof that he was God. He posted signs up in his apartment to that effect. When his wife tried to dissuade him he attempted to strangle her. Upon admission, he was agitated and delusional. The diagnosis



was schizophrenic reaction, paranoid type, acute. He was treated with chlorpromazine 250 mg p.o. q.i.d. for one month. He recompensated during this time. The chlorpromazine was reduced over a seven-day period to 100 mg p.o. q.i.d. He was then discharged to private psychotherapy.

He felt anxious for three weeks but was otherwise asymptomatic. The chlorpromazine dosage was reduced by his therapist to 100 mg p.o. b.i.d. One week later the patient again became agitated and felt he had God-like powers. He was readmitted to the hospital one month after discharge. He was medicated with chlorpromazine 200 mg p.o. q.i.d.; two days later the dosage was increased chlorpromazine 250 mg p.o. q.i.d. The following day he received chlorpromazine 300 mg p.o. q.i.d.; by the fourth day of hospitalization chlorpromazine 350 mg p.o. q.i.d. was required because of agitation.

Three weeks later he was transferred for long term hospitalization. He was no longer delusional but continued to be extremely anxious and restless. This condition persisted despite a maintenance dosage of chlorpromazine 350 mg p.o. q.i.d.

*Case 6.* N.P., a 39 year old married mother of Spanish-Indian descent first became depressed after the birth of her second child. About fourteen months prior to admission, after the child's first birthday, the patient became increasingly withdrawn and preoccupied with ideas of reference. She began to feel that people were discussing her on television and writing about her in the newspapers. She also feared that someone might enter her house at night and harm her children. The diagnosis on admission was schizophrenic reaction, paranoid type, acute. She was treated with chlorpromazine 150 mg p.o. q.i.d. and slowly recompensated over a one month period.

After six weeks she was discharged to the Aftercare Clinic. Upon discharge she was still receiving chlorpromazine 150 mg p.o. q.i.d.

During a clinic visit, two weeks later, she was noted to have a pruritic skin rash. Her medication was changed thioridazine 100 mg p.o. q.i.d. and chlorodiazepoxide 200 mg p.o. q.i.d. Within two weeks she became depressed again and intermittently fearful for the safety of her children. Three days prior to her readmission she discontinued her medication as she had "run out of it." When seen in the Aftercare Clinic she was convinced that people were staring at her. She also felt that her children's lives were in jeopardy. She was very depressed and expressed suicidal ideation. Upon readmission, the clinic medication (thioridazine 100 mg p.o. q.i.d. and chlorodiazepoxide 20 mg p.o. q.i.d.) was continued.

After eight days her mental status remained unchanged. Chlorodiazepoxide was discontinued and trifluoroperazine 5 mg p.o. q.i.d. was instituted. On the twenty-first day after admission, medication was changed to trifluoroperazine 10 mg p.o. t.i.d. and amitriptyline 50 mg p.o. t.i.d. After forty-one days of hospitalization, the patient was discharged, no longer delusional but still somewhat anxious and depressed. She continues on the discharge medication regimen in the Aftercare Clinic.

*Case 7.* C.K., a 71 year old divorced lawyer became depressed four months



prior to admission when he noted that his law practice had diminished considerably. During the week prior to admission he became anorectic, insomniac, irritable, withdrawn, and confused. He became convinced that his financial condition was perilous. The diagnosis upon admission was psychotic depression, with organic brain syndrome.

During the first five days following admission the patient became very regressed requiring aid in all activities, including bodily care. He begged and pleaded not to be sent to a state hospital, and failed to respond to reassurances that no such plan was being considered for him. Neurological evaluation revealed no abnormalities.

On the ninth hospital day, therapy with chlorpromazine 50 mg p.o. t.i.d. and amitriptyline 25 mg p.o. t.i.d. was instituted. Agitation and persecutory ideation continued during the following week. Chlorpromazine dosage was increased to 100 mg p.o. q.i.d.

After one month the patient was calm, less depressed, and free of paranoid ideation. His sensorium was clear. He was discharged to the Aftercare Clinic six weeks after admission, receiving chlorpromazine 300 mg p.o. q.d. He attended the clinic regularly and appeared to be doing well. He pleaded for less frequent clinic appointments. Six months after discharge he was attending the clinic only once a month. Two months prior to his second admission, he refused to attend the clinic and discontinued the medication. He stated that he felt well, and was able to manage his own therapy.

On the morning of his second admission, he was found comatose in his apartment as a result of barbiturate overdose. Upon admission to the Intensive Care Unit, he required a tracheotomy and hemodialysis. Upon regaining consciousness forty-eight hours later, he denied depression and the suicidal attempt, but appeared markedly depressed. A second suicidal attempt was made on the fourth hospital day, the patient using bizarre means for the purpose.

During the following week the patient expressed many persecutory ideas. He felt that the doctors had injected him with bacteria. He remained depressed and intermittently denied and expressed suicidal ideation. At times he was confused and disoriented.

On the sixth hospital day, amitriptyline 25 mg p.o. t.i.d. and trifluoperazine 2 mg p.o. t.i.d. was instituted with chlorpromazine 50 mg p.o. q 2H for agitation. The regimen of medication was changed several times over the next two weeks because of side effects. He was finally maintained on chlorpromazine 50 mg p.o. t.i.d.

By the fourth week of hospitalization on chlorpromazine 50 mg p.o. t.i.d. his sensorium was clear; he had no further persecutory delusions and was only slightly depressed.

*Case 8.* M.F., an 18 year old single, female, high-school student was admitted to the Gynecology Service because of oligomenorrhea. Gynecological and endocrinological evaluations were almost completed, but as the time for discharge approached, the patient became very anxious and spoke of having a bird phobia. She also expressed ideas of reference and claimed auditory

hallucinations. She was transferred to the Psychiatric Service where the diagnosis of schizophrenic reaction, paranoid type was made. Upon transfer, the patient became very anxious and insisted that her mother sign her out of the hospital.

She was seen twice in the Gynecology Clinic by the Psychiatric Liaison Service to prepare her to accept in-patient care. It was then possible to re-hospitalize her within two weeks. Upon readmission the patient was depressed and agitated. From the third hospital day she received chlorpromazine 50 mg p.o. q.i.d.; by the seventh day, the dosage was increased to chlorpromazine 125 mg p.o. q.i.d. The patient continued with ideas of reference and severe anxiety. The dosage of chlorpromazine was increased to 200 mg p.o. q.i.d.

By the end of the first month of hospitalization, the patient appeared progressively less anxious and was able to tolerate leaving the hospital for brief periods of time. She returned to high school while still hospitalized. Thereafter she was discharged to the Aftercare Clinic. She had spent six weeks in the hospital.

At her first clinic visit the patient was very anxious and felt, again, that people were watching her. She had been unable to attend school for the two days prior to the clinic visit. She had discontinued medication upon discharge because, she said, she had been feeling so well. Chlorpromazine 100 mg p.o. q.i.d. was reinstituted. The following week the patient was able to attend school and felt comfortable on the street. She has continued to do well since this time.

TABLE I  
*Course of Phenothiazine Therapy*

Patient	Drug	Dosage	Length of Therapy	Time from Discontinuation of Therapy to Decompensation	Time from Reinstitution of Therapy to Re-compensation
M.W.	chlorpromazine	400 mg qid	4 wks.	18 hrs.	10 days
S.L.	chlorpromazine	100 mg qid	2 wks.	48 hrs.	14 days
	trifluoperazine	5 mg qid	5 wks.	7 days	7 days
N.G.	chlorpromazine	100 mg qid	1 yr.	2 wks.	48 hrs.
C.A.	chlorpromazine	50 mg tid	5 days	24 hrs.	13 days
M.W.	chlorpromazine	250 mg qid	4 wks.	1 wk.	3 weeks still severely decompensated
N.P.	chlorpromazine	150 mg qid	8 wks.	2 wks.	41 days
C.K.	chlorpromazine	100 mg tid	24 wks.	8 wks.	4 wks.
M.F.	chlorpromazine	50 mg qid	6 wks.	7 days	7 days

## DISCUSSION

It appears that when antipsychotic medication was interrupted following a first acute psychotic decompensation a significant number of patients experienced a florid relapse. Similar situations are very familiar in the treatment of cardiac decompensation with digitalis, collagen disease with steroids or epilepsy with anticonvulsants. Experience in the treatment of these diseases has indicated that medication should be gradually reduced rather than rapidly discontinued and that wherever necessary a substitute drug should be introduced. It is likely that acutely psychotic patients regulated on antipsychotic medication might best be managed in the same manner. In the treatment of many diseases it is necessary to carefully observe the patient for recurrence of symptomatology after discontinuation of medication so that in case of relapse appropriate measures can be speedily reinstituted. It seems that this procedure also applies in the case of acutely psychotic patients whose antipsychotic medication is being discontinued.

In the treatment of the diseases already mentioned patients are usually cautioned of the imperative need to continue the medication until otherwise advised because of possible untoward reaction to the interruption of medication. It appears that the psychiatrist should similarly advise the patient recovering from an acute psychotic reaction. As in the management of other illness in patients whose cooperation seems doubtful, the family should also be informed of the need to follow the prescribed drug regimen.

Controlled studies on statistically significant samples of acutely psychotic patients receiving phenothiazine therapy are needed to determine whether the rate of decompensation is lower in patients maintained for longer periods on medication or among patients whose medication is gradually rather than abruptly discontinued.

## SUMMARY

Brief histories of eight patients who experienced psychotic decompensation upon discontinuation of their antipsychotic medication have been presented. The course of treatment is summarized in Table I. Originally, with phenothiazines, hospitalization and psychotherapy each appeared recompensated within periods varying from forty-eight hours to six weeks. In each case, medication was then discontinued either by the therapist or the patient. This took place from forty-eight hours to one year after recompensation and each patient experienced a florid exacerbation of symptoms with overt psychotic manifestations. Antipsychotic medication was rapidly reinstituted in all cases and remission occurred within forty-eight hours to six weeks. Six of the eight patients required rehospitalization.

This preliminary study suggests that within the first year following psychotic decompensation, antipsychotic medication be discontinued only under close supervision of the psychiatrist. This should be done preferably in a gradual manner, rather than abruptly because of the danger of an acute psychotic relapse.

## REFERENCES

1. Massie, S. P.: The Chemistry of Phenothiazine. *Chem. Rev.*, 54: 797, 1954.
2. Delay, J., Deniker, P., and Harl, J. M.: Utilisation en Therapeutique d'une phenothiazine d'Action Centrale Elective (4560RP) *Ann. méd.-psychol.*, 110: (2) 112, 1952.
3. Ruesch, J., Brodsky, C., and Fischer, A.: The Acute Nervous Breakdown. *Arch. Gen. Psych.*, 8: 197, 1963.
4. Tuteur, W., Stiller, R., and Glotzer, J.: The Discharged Mental Hospital Chlorpromazine Patient. *Dis. Nerv. System*, 20: 512, 1959.
5. Gittelman, R., Klein, D., and Pollack, M.: Effects of Psychotropic Drugs on Long Term Adjustment. *Psychopharmacopia*, 5: 317, 1964.
6. Caffey, E., Diamond, L., and Frank, T.: Discontinuation or Reduction of Chemotherapy in Chronic Schizophrenies. *J. Chron. Dis.*, 17: 347, 1964.
7. Winkleman, N.: A Long Term Investigation of Chlorpromazine. *Am. J. Psychiat.*, 116: 865, 1960.
8. Rosati, D.: Prolonged High Dosage Medication in Chronic Schizophrenies. *Dis. Nerv. System*, 24: 683, 1963.
9. Lehman, H.: Psychopharmacology. *Ohio Med. J.*, 59: 1091, 1963.
10. Forrest, F. M., Geiter, C. W., Snow, H. L., and Steinbach, M.: Drug Maintenance Problems of Rehabilitated Mental Patients. *Am. J. Psychiat.*, 121: 33, 1964.
11. Gantz, R., and Birkett, M.: Phenothiazine Reduction as a Cause of Rehospitalization. *Arch. of Gen. Psych.*, 12: 586, 1965.

# Obstruction of the Outlet of the Fourth Ventricle in an Adult

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Obstruction of the orifices of communication between the fourth ventricle and the subarachnoid space (the foramina of Magendie and Luschka) manifested during infancy and childhood is a well-known clinicopathological entity. This condition, usually referred to as the Dandy-Walker Syndrome (1), may be associated with symmetrical hydrocephalus, dilated fourth ventricle, and enlarged posterior fossa with upward displacement of the tentorium. Mental retardation is frequently present.

During adult life obstruction of the outlet of the fourth ventricle may be the result of a variety of less clearly defined processes. In addition to examples of Dandy-Walker syndrome which first become manifest in adulthood, post-infectious arachnoiditis and ependymal or arachnoid cysts (2) have been implicated as causing occlusion of the foramina of Magendie and Luschka in adults. In those instances which are not preceded by definite infection or are not associated with agenesis of the vermis or other posterior fossa anomalies, it is difficult to determine whether the obstruction of the orifices of the fourth ventricle is congenital or inflammatory.

The following case manifested initial symptoms late in life. There were no associated cysts or apparent anomalies of the cerebellar hemispheres or vermis.

## CASE REPORT

A 67 year old right-handed male mechanic entered The Mount Sinai Hospital in 1963. Four weeks prior to admission he began to have headaches, anorexia, weight loss, mental changes, difficulty with gait, and slurring of speech.

On admission the general physical examination was unremarkable. The neurological examination revealed a moderate organic mental syndrome. There was nystagmus on lateral and upward gaze. The speech was dysarthric. His gait was unsteady; however, coordination of the extremities was satisfactory. Power of extremities and sensation were normal. The deep tendon reflexes were active; the plantar responses were flexor bilaterally.

The past history included a course of electroshock therapy fifteen years previously for depression.

Laboratory studies and blood serology were normal. A lumbar puncture revealed an initial pressure of 140 mm of water; the cerebrospinal fluid protein was 42 mg per cent. Spinal fluid serology and colloidal gold tests were negative. The skull x-rays were normal. X-ray of the chest revealed emphysema and

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healed fibrocalcific disease. Electroencephalography demonstrated bilateral cerebral dysfunction with focal accentuation in the left temporal region.

Pneumoencephalography was carried out on two occasions but no filling of the ventricular system could be achieved; the cisterna magna and basal cisterns were visualized and were unremarkable. Left carotid arteriogram demonstrated moderate hydrocephalus. Right and left vertebral angiograms were normal. The pantopaque myelencephalogram (Fig. 1) revealed filling of the cisterna magna but pantopaque did not enter the ventricular system (3). Pantopaque ventriculography (Fig. 2) was carried out. There was symmetrical hydrocephalus with enlargement of the third and fourth ventricles. Pan-



FIG. 1. Pantopaque myelencephalogram. There is filling of the cisterna with pantopaque. No pantopaque enters the ventricular system.

topaque readily entered the fourth ventricle but did not flow into the cisterna magna despite positioning of the patient in the erect position.

A posterior fossa exploration was carried out. The dura over the cerebellar hemispheres was moderately tense. The cisterna magna appeared normal. There was no cyst of the posterior fossa or asymmetry of the cerebellar hemispheres. Exploration of the cerebellar hemispheres encountered no abnormal tissue. The tonsils were markedly adherent and could be separated only by blunt dissection. Despite separation of the cerebellar tonsils no fluid drained from the fourth ventricle. The inferior vermis was incised and the fourth ventricle entered. Pantopaque, which had been previously instilled into the frontal horns, refluxed from the opening. The fourth ventricle and aqueduct of Sylvius were markedly enlarged. Saline introduced into the right lateral ventricle through an occipital burr hole refluxed into the fourth ventricle. A Torkildsen procedure was carried out. Biopsies of the arachnoid over the cisterna magna and vermis were normal.

Following surgery the patient became more responsive and less confused although his gait remained moderately ataxic. He was discharged to his home. One year after surgery he expired. An autopsy could not be obtained.

#### DISCUSSION

Dandy (4) in 1921 reported two cases of occlusion of the foramina of Magendie and Luschka in adults. In one instance "the foramen of Magendie was tightly sealed by adhesions which, however, were not present over the lobes of the cerebellum. The cerebellum and medulla were tightly adherent, thus effectively preventing the fourth ventricle from bulging between these structures." Dandy believed that the etiology was infectious. Horrax

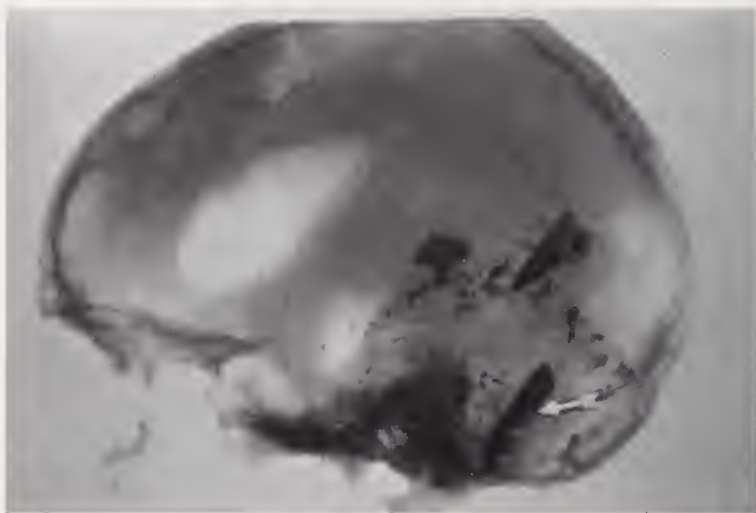


FIG. 2. Pantopaque ventriculogram (polaroid film). Symmetrical hydrocephalus. Arrow points to pantopaque in the fourth ventricle. Pantopaque does not exit from the fourth ventricle.

(5) also described examples which presented clinically as posterior fossa tumors and were found to have "inflammatory thickening of the arachnoid membrane of the cerebellar and basal cisternae."

David and associates (6) reported two cases very similar to ours. They pointed out that the outlet of the fourth ventricle may be occluded by intertonsillar adhesions of the vermis which "are sometimes so marked that unblocking of the fourth ventricle can be obtained only after section of the vermis and ablation of the tonsils."

In adults the condition presents with a rapid or slow onset of signs and symptoms of increased intracranial pressure. Headaches, vomiting, papilledema and mental changes are not uncommon. Dysmetria, ataxia, nystagmus and, at times, cranial nerve involvement point to pathology in the posterior fossa.

The diagnosis of obstruction of the foramina of Magendie and Luschka

can be made by the use of combined pneumoencephalography and ventriculography. The pneumoencephalogram shows non-filling of the ventricular system. The ventriculogram may demonstrate symmetrical enlargement of the lateral ventricles with a dilated third and fourth ventricle which are not shifted from the midline. Air does not enter the subarachnoid space from the fourth ventricle. Excellent contrast was achieved in our case by the use of pantopaque ventriculography and myeloencephalography. During pantopaque ventriculography oil did not escape from the fourth ventricle even when the patient was positioned in the erect manner. Therefore, the diagnosis of obstruction of the outlet of the fourth ventricle could be made pre-operatively.

At surgery there was no neoplasm, cyst, or congenital anomaly. The tonsils were adherent and it was necessary to section the inferior vermis, as advocated by Pasztor (7), to gain entrance into the fourth ventricle. Section of the vermis seems particularly indicated when the usual anatomy of the area of the foramina of Magendie and Luschka is so distorted that the foramina are virtually non-existent. Although a communication was established between the ventricular system and the subarachnoid space, a Torkildsen procedure was performed in order to provide an additional pathway for the cerebrospinal fluid circulation in view of the late recurrences which have been noted in the literature (6, 7).

#### SUMMARY

A case of obstruction of the foramina of Magendie and Luschka occurring late in life is reported. The diagnosis was established pre-operatively by the combined use of myeloencephalography and pantopaque ventriculography. The operative procedure consisted of separation of tonsillar adhesions, section of the vermis, and establishment of a Torkildsen shunt.

#### REFERENCES

1. Benda, C. E.: The Dandy-Walker Syndrome or the So-Called Atresia of the Foramen Magendie. *J. Neuropath. & Exper. Neurol.*, 13: 14, 1954.
2. Alvord, E. C., and Marcuse, P. M.: Intracranial Cerebellar Meningo-Encephalocoele (Posterior Fossa Cyst) Causing Hydrocephalus by Compression at the Incisura Tentorii. *J. Neuropath. & Exper. Neurol.*, 21: 50, 1962.
3. Mones, R., and Werman, R.: Pantopaque Myeloencephalography. *Radiology*, 72: 803, 1959.
4. Dandy, W. E.: The Diagnosis and Treatment of Hydrocephalus Due to Occlusion of the Foramina of Magendie and Luschka. *Surg. Gynec. & Obst.*, 32: 112, 1921.
5. Horrax, G.: Generalized Cisternal Arachnoiditis Simulating Cerebellar Tumor. *Arch. Surg.*, 9: 95, 1924.
6. David, M., Djahanchahi, A. and Aboulker, J.: L'Obstruction des Trous de Luschka et de Magendie. *Neurochirurgie*, 7: 210, 1962.
7. Pasztor, E.: Über eine Modifikation des chirurgischen Eingriffes bei entzündlichem Foramen-Magendie-Verschluss. *Neurochirurgia*, 3: 59, 1960.

## **A Case of Granulomatous Ileocolitis in a Child: Report of an Unusual Complication**

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Inflammatory conditions of the large and small bowel are relatively infrequent in children and adolescents compared to their common occurrence in the adult population. Thus, regional enteritis, ulcerative colitis and ileocolitis are rarely seen below the age of sixteen. Combinations of inflammatory diseases of the ileum and colon have recently been carefully classified and differentiated pathologically and radiographically (1, 2, 3).

The case to be presented is that of granulomatous ileocolitis in a 13 year old girl with a very unusual postoperative complication. It is because of the rarity of this lesion and the very unusual nature of the complication that the case is presented.

### **CASE REPORT**

On January 12, 1964, a 12 year old girl was admitted to the hospital with a 24 hour history of abdominal pain. The patient had chills and fever for one week prior to admission and had been given a broad spectrum antibiotic empirically. Temperature on admission was 102°. The white blood count was 17,500. Physical examination on admission revealed a tender mass in the right lower quadrant, with rebound tenderness. Chest X-ray was negative. Abdominal X-ray revealed diffuse haziness in the right half of the abdomen and pelvic cavity.

At exploration, through a McBurney incision, a right lower quadrant abscess was found and was drained. The appendix could not be found. A portion of omentum was removed for biopsy. Culture of the pus revealed *B. coli* and enterococcus. Biopsy disclosed an acutely and chronically inflamed omentum. The patient was given chloromycetin postoperatively. Her convalescence was benign and the patient was discharged on January 15, 1964. The drain was removed on January 21, 1964. The drainage site did not close during the next 6 months, after which the patient was readmitted for further investigation.

The patient was admitted for the second time on July 13, 1964 for investigation of a persistent fistulous tract in the area of the previous drain site. During the previous 6 months following discharge from the hospital, she had experienced intermittent attacks of lower abdominal pain. Physical examination on admission revealed a palpable mass in the right lower quadrant with a draining sinus in the middle of it. Peristaltic waves were visible in the right lower quadrant. A small bowel series, barium enema examination and fistulogram were done. The small bowel series revealed areas of dilatation in the mid and distal jejunum. The entire ileum appeared dilated and the dis-

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tal portion displayed marked distension with ulceration throughout a segment approximately 20 cm long. The involvement was contiguous with the ascending colon (Fig. 1B). The fistulogram revealed contrast material passing into the ascending colon showing marked nodularity and linear ulcerations. The findings were those of a combined regional ileitis and granulomatous colitis. Sigmoidoscopy to 6 inches revealed normal rectal mucosa.

On July 27, 1964, the patient had a temperature of 105°F. with vomiting and abdominal pain. She was placed on chloromycetin and polycillin and improved rapidly. The patient was discharged on July 31, 1964. Intervention was not deemed advisable because of the extensive disease in both the small and large bowel.

The patient was readmitted on August 2, 1964 for further evaluation of her disease. On August 6, 1964 she had noted vomiting, severe abdominal pain, abdominal distension and right lower quadrant pain and tenderness. Flat film of the abdomen revealed mechanical small bowel obstruction with multiple air fluid levels present (Fig. 1A). A Cantor tube was passed but failed to decompress the small bowel. The patient's temperature ranged between 101° and 102°F. Her hemoglobin was 8.8 Gm%. On August 10, 1964, after preoperative preparation with antibiotics and blood, the patient was explored. The distal 2½ to 3 feet of ileum and the entire ascending colon and hepatic flexure showed marked thickening of the bowel and mesentery, with numerous enlarged lymph nodes. An ileotransverse colostomy, end-to-side, with exclusion of the distal ileum, was performed. Frozen section of an enlarged lymph node showed acute inflammation. The ileum biopsied at the level of the anastomosis showed only slight edema and congestion. Her postoperative course was uneventful and the patient was discharged on August 20, 1964.

The patient was readmitted to the hospital two months later. She had been well and gained about 20 pounds until two weeks prior to hospitalization, at which time she noted enlargement of the abdomen associated with cramp-like right lower abdominal pains. By the time she was seen in the Follow-up Clinic the cramps had become more severe and unremitting and a mass was obvious on palpation in the right lower quadrant.

On admission, the patient did not appear acutely nor chronically ill. She was afebrile and presented no unusual physical signs except for a large oval mass about 10 cm in longitudinal axis occupying almost all of the right abdomen. Flat film of the abdomen (Fig. 2) revealed a homogeneous mass occupying the right side of the abdominal cavity and displacing the small and large intestines to the left. Further diagnostic investigation was curtailed by the observation that the abdominal mass was rapidly increasing in size.

The patient was re-explored without delay with a diagnosis of intra-abdominal abscess possibly due to bowel fistulization. At operation (Fig. 3), a large football-sized mass of bowel was encountered occupying most of the right half of the abdominal cavity. This mass comprised the terminal excluded loop of ileum which had undergone ileo-ileal intussusception carrying with the intussusception the small intestine and a portion of the large intestinal mesen-



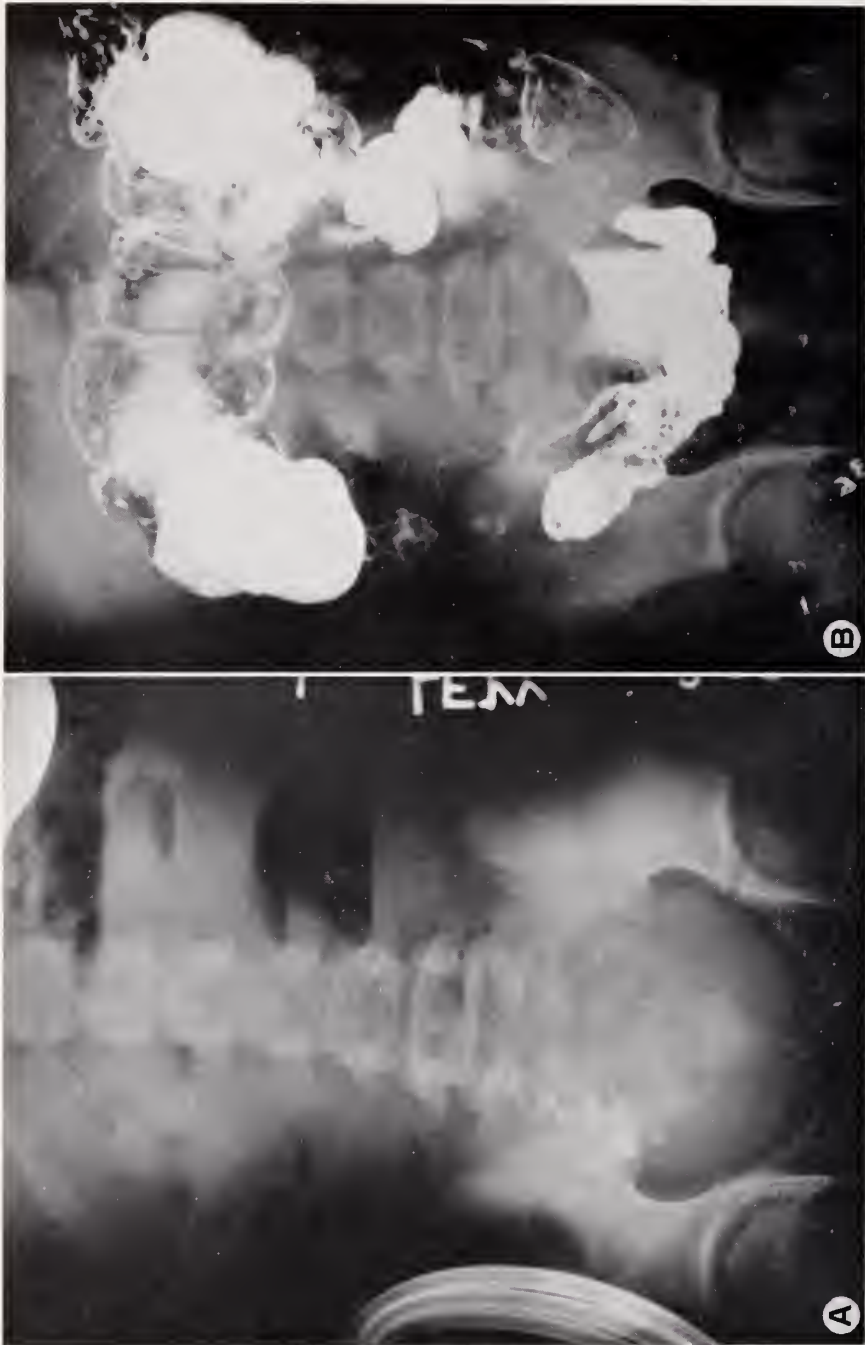


FIG. 1a. Flat film of the abdomen prior to exploration on the third hospitalization showing mechanical small bowel obstruction.  
FIG. 1b. Barium enema disclosing typical granulomatous lesions of the terminal ileum and the ascending colon.



FIG. 2. Flat film of the abdomen disclosing a large homogeneous shadow occupying the right half of the abdominal cavity and displacing the intestines to the left.

tery. The intussusciens had perforated into the intussusceptum. The region of the previous ileotransverse colostomy was congested, indicating beginning vascular interference due to mesenteric compression.

The intussusception was carefully reduced manually and the excluded ileal loop resected. There was no other evidence of persistent inflammatory dis-

ease in the small or large bowel. The abdomen was closed without drainage. Pathological report of the specimen showed healed terminal ileitis.

The patients's post-operative course was uneventful, and she was discharged two weeks after surgery. During the ten months following discharge, the patient was seen at regular intervals and has remained well.



FIG. 3. Operative photograph showing dilated terminal excluded loop with ileo-ileal intussusception.

#### DISCUSSION

Coexisting inflammatory disease of the small and large bowel is occasionally seen if a careful search of the large bowel is made in cases of regional ileitis and a careful search of the small bowel is made in cases of ulcerative colitis. In classifying these cases of coexisting disease, Yarnis, *et al.* (1) adequately separated the various pathologic types according to the following schema: "Combined ileocolitis" signifies the presence of granulomatous ileitis and ulcerative colitis. When granulomatous ileitis is combined with granulomatous colitis, the term "granulomatous ileocolitis" is used. These two types can be differentiated both radiographically (2, 4, 5, 6, 7) and pathologi-

cally. Granulomatous ileocolitis is a much less frequent lesion than combined ileocolitis. In 60 cases of ileocolitis reported by Yarnis (1), only 2 cases were reported as granulomatous ileocolitis, while 58 were combined ileocolitis. Lindner, *et al.* (2) report 37 cases of granulomatous disease of both colon and small bowel. Lockhart-Mummery, *et al.* (3) report 22 cases of granulomatous disease of large bowel and ileum (30%) of 75 patients with granulomatous colitis.

The granulomatous nature of regional ileitis and the exudative inflammatory process of ulcerative colitis are seen in combined ileocolitis with the usual x-ray manifestations of two separate processes. Thus, the small bowel presents an x-ray picture (8) of narrowing of the lumen, rigidity, inflammatory polyps, mucosal ulcerations, skip areas, internal and external fistulae and stenosis of the distal ileum with proximal dilatation. The large bowel in combined ileocolitis shows a process which is usually diffuse, extending to the splenic flexure and mid-descending colon. There is slight to moderate rigidity and absent or distorted haustral markings. Ulceration and shortening of the colon are usually seen. The lesions in the colon are ordinarily not in continuity with the lesions in the terminal ileum. In granulomatous colitis, there is frequently a short segment involved in continuity with the ileal lesion. The colon shows marked narrowing and rigidity rather than ulceration.

Although some investigators consider granulomatous and ulcerative colitis as manifestations of the same basic inflammatory disease (9), granulomatous colitis now appears to be an established pathological diagnosis (3, 10). On examination, there are often skip areas of disease, with intervening areas of normal bowel, along the length of the colon. The ulcerations are long, longitudinal ulcerations and may extend deeply to form fistulae. Considerable narrowing of the lumen and stricture formation may be present. Ragged mucosal tags and inflammatory polyps with stalks are rare in granulomatous colitis.

Granulomatous colitis, in contrast to ulcerative colitis, rarely presents with rectal bleedings and tends to start in early adult life. Diarrhea, abdominal cramps and fever are common and fistulae are often seen and are usually in the ileum rather than in the colon itself. As reported by Lindner (2), the patients with granulomatous colitis have followed a more chronic and unremitting course than those with ulcerative colitis, acute fulminating episodes being extremely rare.

Although steroids are valuable in controlling symptoms in granulomatous colitis, as they are in ulcerative colitis, surgery is necessary for complications of the disease. Three-quarters of the patients in Lindner's series were operated upon for incomplete intestinal obstruction and/or for chronic toxicity associated with the condition.

Granulomatous colitis in childhood or adolescence is rare, in comparison to the more frequent occurrence of regional enteritis or ulcerative colitis. Of 75 patients with "Crohn's Disease of the Large Intestine" reported by Lockhart-Mummery, two children are reported, both aged 10. No mention is made as to whether these children only had disease of the colon or granulomatous ileo-



colitis. Of 44 patients with granulomatous colitis reported by Lindner (2), the youngest patient was 16 years of age. Rudle and Keats (11) report on 15 cases of granulomatous ileocolitis in pre-adolescent and adolescent children represents the largest reported series of this entity in children. Ten of these patients came to surgery. Sutcliffe (12) reported 5 cases of granulomatous colitis in children, varying in age from 7 to 19 years. His cases were all confined to the colon.

The case presented satisfied the criteria of granulomatous ileocolitis in all respects, although the synchronous nature of the ileocolitis cannot be ascertained. Since no radiographic studies of the small and large bowel were performed for 6 months after the original exploration, we cannot be sure that the colitis did not develop after the ileitis had been present. However, in cases of metachronous ileocolitis (1), the colitis developed after an ileotransverse colostomy had been performed.

Certainly the failure of a drainage tract to close after surgery is often seen in cases of regional ileitis or ulcerative colitis. It is not uncommon for a draining site to close completely, or for an appendectomy to heal without incident, although the failure of this to occur should arouse suspicion.

The indication for surgery in this girl was repeated bouts of intestinal obstruction and evidence of active infection in the abdomen. The findings at operation confirmed this diagnosis, and ileotransverse colostomy with exclusion was performed. With the development of acute symptoms two months postoperatively, the diagnoses entertained were either blind loop syndrome or reactivation of the disease in the excluded ileum. The finding of intussusception of the excluded ileum into itself, with intraluminal perforation, is very unusual and has rarely been reported. The reason for the excluded suture line acting as the lead point for the intussusception is unclear, nor has any lesion been demonstrated pathologically at this point to account for it. The occurrence of this type of complication may be taken as an argument for the performance of resection rather than exclusion at the original operation.

#### SUMMARY

An unusual case of a 13 year old girl with granulomatous ileocolitis is discussed. A very unusual complication, intussusception of an excluded loop of ileum into itself, following ileotransverse colostomy with exclusion is presented.

#### REFERENCES

1. Yarnis, H., Marshak, R. H. and Crohn, B. B.: Ileocolitis. *JMA*, 164: 7-13, 1957.
2. Lindner, A. E., Marshak, R. H., Wolf, B. S. and Janowitz, H. D.: Granulomatous colitis. *New Eng. J. Med.*, 269: 379-385, 1963.
3. Lockhart-Mummery, H. E. and Mason, B. C.: Crohn's Disease of the Large Intestine. *J. Brit. Soc. Gastroenterology*, 5: 493-509, 1964.
4. Yarnis, H.: Symposium on Regional Ileitis: Syndrome of Combined Ileocolitis. *J. Mt. Sinai Hosp.*, 22: 159-169, 1955.
5. Wolf, B. S. and Marshak, R. H.: Granulomatous Colitis: Roentgen Features. *Amer. J. Roent.*, 88: 662-670, 1962.



6. Marshak, R. H., Wolf, B. S. and Eliasoph, J.: Segmental colitis. *Radiology*, 73: 707-716, 1959.
  7. Yarnis, H. and Crohn, B. B.: Segmental Colitis. *Gastroenterology*, 38: 721-728, 1960.
  8. Marshak, R. H. and Wolf, B. S.: Roentgen Findings in Regional Enteritis. *Amer. J. Roent.*, 74: 1000-1014, 1955.
  9. Lumb, G. and Protherol, R. H.: Ulcerative Colitis: Pathologic study of 152 Surgical Specimens. *Gastroenterology*, 34: 381-407, 1958.
  10. Comes, J. S. and Stecker, M.: Primary Crohn's Disease of Colon and Rectum. *J. Brit. Soc. Gastroenterology*, 2: 189-201, 1961.
  11. Rudle, W. and Keats, T. F.: Granulomatous colitis in Children. *Radiology*, 84: 24,
  12. Sutcliffe, V.: Crohn's disease of the colon. *Brit. J. Radiol.*, 36: 27-32, 1962.
- 1965.

# The Clinical Use of Intrathecal Methylprednisolone Acetate\* Following Pneumoencephalography and Myelography\*\*

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## INTRODUCTION

This investigation was concerned with the effect of intrathecal methylprednisolone acetate (Depo-Medrol) upon the symptoms following fractional air pneumoencephalography, and Pantopaque myelography in an attempt to find a more effective therapeutic agent in the treatment of these post-procedural syndromes.

The first part of this study investigated the effect of Depo-Medrol on post-pneumoencephalogram symptoms. It is well-known that the symptoms of headache, nausea, vomiting, light-headedness, etc., associated with pneumoencephalography are very distressing to the patient. Studies have correlated the amount of cerebrospinal fluid leakage (1), amount of air injected (2), and presence of ventricular dilatation (2) with the severity of post-pneumoencephalogram morbidity. There is as yet no effective treatment for the headache which follows the pneumoencephalogram. Analgesics, fluids, oxygen, and time, principally the latter, terminate the patients' sufferings in a number of days. Because of the dramatic ameliorative properties of methylprednisolone in preventing post-lumbar puncture headaches (3), it was decided to evaluate its effect on post-pneumoencephalogram headaches.

## PART I

### *Method*

One hundred and twenty patients receiving fractional air pneumoencephalography were divided in serial rotation into one of four groups of 30 patients each. All patients were premedicated with 0.4 mgm atropine, subcutaneously, only. At the completion of air injection before withdrawal of the needle, Group I received intrathecal instillation of 10 cc 0.9% saline; Group II received 40 mgm methylprednisolone acetate with polyglycol vehicle in 10 cc 0.9% saline; Group III received 0.1 cc polyglycol vehicle† in 10 cc 0.9% saline; and Group IV received no injection. An 18 gauge lumbar puncture needle was used in all cases. Pneumoencephalograms were performed by several neurology residents involving variations in technique, amount of air injected, length of time in the X-ray department, ventricular dilatation, and upon patients

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with varying severity of organic mental syndrome. All patients able to undergo air pneumoencephalography were included in this study. All patients were examined the day of the pneumoencephalogram by several observers and daily thereafter, and were questioned about their symptoms, with emphasis on headache as the most consistently reliable manifestation of postpneumoencephalographic symptoms.

### Results

Table I shows that while the age ranges are similar for the four groups, the distribution of sexes is unequal with a preponderance of females. However, an analysis of the mean duration of headache in hours reveals that while females had symptoms for a longer period of time after pneumoencephalography (45–60 hours for females, 40–50 hours for males), the difference was not statistically significant. Therefore, the mean durations of headaches for males and females were combined. It is apparent that the amounts of air used were simi-

TABLE I  
*Pneumoencephalography*

Group	Age	Sex		Mean duration of symptoms (hours)			Mean volume air (cc)	No. dilated ventricles	Mean Duration of symptoms (hours)
		M	F	Male	Fe-male	Com-bined			
I. Saline	45	14	16	44	48	46	65	8	18
II. Depo-Medrol	44	11	19	10.5	15	13.5	67	7	6
III. Vehicle	46	13	17	40	45	43	72	8	20
IV. No injec.	47	12	18	50	60	47	70	10	25

lar and the numbers of patients with dilated ventricles were also equivalent. There is, however, a statistically significant difference ( $P < .05$ ) in mean duration of post-pneumoencephalogram headache between patients with dilated ventricles (18–25 hours) and those with normal ventricular systems (43–47 hours) using the “t” test. Therefore, these patients were eliminated from the general group and were analyzed separately. In the remainder of the groups, it can be seen that the mean duration of post-pneumoencephalogram symptoms in patients receiving methylprednisolone is statistically significantly shorter (13.5 hours,  $P < .001$ ) than that in the control groups (43–47 hours). There was no significant difference in duration of headache between the patients in the three control groups. It was also found that patients with dilated ventricles receiving methylprednisolone had a statistically significantly shorter duration of headache (6 hours,  $P < .01$ ) than those not receiving methylprednisolone (18–25 hours). The remaining three control groups of patients with dilated ventricles did not differ significantly from one another in mean duration of headache. It should be noted that while patients in the methylprednisolone group complaining of headache received no other medication, those

in the control groups received aspirin, Darvon, caffeine sodium benzoate, Compazine, etc. Therefore, the mean duration of headache in these latter groups is not representative of the true length of post-pneumoencephalogram symptoms and conceivably these patients would have had symptoms for an even longer time than they did. Nevertheless, these control groups still had a significantly longer duration of post-pneumoencephalogram symptoms as compared to the group receiving methylprednisolone.

## PART II

### *Method*

The second part of this investigation is concerned with the efficacy of intrathecal methylprednisolone instillation following Pantopaque myelography in the prevention of post-myelogram symptoms, including back pain with radiation into the leg, paresthesiae, headaches, and stiff necks. One hundred and

TABLE II  
*Myelography*

Group	Age	Sex		Mean duration of symptoms (hours)	Mean volume pantopaque in Mean volume pantopaque out	Incidence symptoms %
		M	F			
I. Saline	48	12	18	25	18/12	36
II. Depo-Medrol	44	12	18	5	18/12	10
III. Vehicle	50	16	14	28	18/15	33
IV. No injec.	48	14	16	30	18/10	40

twenty patients receiving Pantopaque myelography, lumbar as well as cervical, were divided in serial rotation into four groups. All patients were premedicated with 0.4 mg atropine, subcutaneously, only. At the completion of the myelogram, after removal of the Pantopaque, Group I received intrathecal instillation of 10 cc 0.9% saline; Group II received 40 mg methylprednisolone acetate with polyglycol vehicle in 10 cc 0.9% saline; Group III received 0.1 cc polyglycol vehicle in 10 cc 0.9% saline; and Group IV received no injection. An 18 gauge lumbar puncture needle was used in all cases. All patients were examined the day of the myelogram by several observers and daily thereafter, and were questioned about back pain, paresthesiae, stiff neck and headache as well as bowel and bladder difficulties.

### *Results*

Table II shows the age and sex distribution among the four groups with a similar preponderance of females as was noted in Part I of this paper. Again the mean durations of symptoms following myelography for males and females were combined as they were not statistically significantly different from one another. As can be seen from Table II, the mean duration of symptoms in

the group receiving methylprednisolone (5 hours) is statistically significantly less than the mean duration of symptoms in the three control groups (25-30 hours) by the "t" test ( $P < .001$ ). The per cent incidence of symptoms in the group receiving methylprednisolone was also significantly less (10%) than the per cent incidence of symptoms in the three control groups (33-40%). Again, the symptomatic patients in the control groups received analgesics and in many cases parenteral or oral steroid therapy after the first 24 hours, so that the mean duration of post-myelogram symptoms would probably have been even longer had these patients remained untreated.

#### DISCUSSION

Davidoff and Dyke (2) analyzed the incidence and duration of post-pneumoencephalogram symptoms and found that three-quarters of the patients had symptoms at the end of twenty-four hours, less than one-half had symptoms at the end of forty-eight hours, and one-third had symptoms after seventy-two hours. They also found that the duration of post-pneumoencephalogram symptoms was directly proportional to the amount of gas used. Those patients receiving 30-60 cc of gas had symptoms for an average of 1.9 days; those receiving 60-90 cc had symptoms for an average of 2.5 days, while patients receiving 90-120 cc had symptoms for an average of 3.3 days. These authors also found that 15 patients with dilated ventricles receiving an average of 91 cc of air had symptoms of somewhat shorter duration (1.9 days) than 28 patients with normal ventricular systems receiving an average of 63 cc of air (2.25 days). Our figures for mean duration of symptoms for those patients receiving 60-90 cc of air are quite similar to those found by Davidoff and Dyke (2), whereas our patients with dilated ventricles had a mean duration of symptoms about one-half as long as those in their study. Those patients without dilated ventricles receiving methylprednisolone had a mean duration of symptoms about one-quarter of those in the above-mentioned study, while our patients with dilated ventricles receiving methylprednisolone had a mean duration of symptoms about one-eighth of those in their study.

Kornreich (4) found that 95% O<sub>2</sub> administered in a tent was associated with the disappearance of all symptoms in 2-2½ days, while Von Storch (5) and others (6) found that a careful program of anesthesia, pre-medication, control of cerebrospinal fluid loss, sedatives, fluids and 95% O<sub>2</sub> would lessen the duration of post-pneumoencephalogram symptoms. No data as to the duration of symptoms was given, however.

Since intrathecal administration of methylprednisolone causes such a marked reduction in duration of symptoms (13.5 hours) compared to other therapeutic regimens, it would seem to be the single most effective agent for this purpose.

Concerning myelography and its attendant complications, Mason and Raaf (7) found that fever, meningismus and headache appeared within five to twenty-four hours after myelography and lasted a variable length of time. Smith and Ross (8) treated meningeal inflammatory response induced by Pantopaque with steroids with good results. Davies (9) found the incidence



of post-myelographic reactions to be 60% with 56/70 patients having immediate reactions while 14/70 patients had chronic reactions. In these patients, contrast material was not removed from the subarachnoid space.

Our data show a lower incidence of post-myelographic symptoms varying between 33–40% of control patients. However, all patients had attempted complete removal of contrast material. As might be predicted from Smith and Ross' results, our patients treated with methylprednisolone had a markedly reduced incidence of symptoms (10%) and duration of symptoms (5 hours) as compared to control groups.

The mechanism of action of methylprednisolone in these circumstances is completely unknown and explanations involving anti-inflammatory effects of the steroid are speculative. Of considerable interest is its effectiveness in abbreviating the duration of symptoms following the injection of foreign material, be it air or Pantopaque. These previously difficult and painful procedures can be made much less traumatic for the patient and his hospital stay may be considerably shortened. Methylprednisolone is, however, no panacea, and a few attempts to treat post-pneumoencephalogram symptoms after they have fully developed have met with mediocre success. Post-myelographic symptoms seem to be more amenable to treatment even some days after the procedure. There have been occasional reports (10, 11) of patients who have undergone pneumoencephalography or myelography, received intrathecal instillation of methylprednisolone and were asymptomatic for forty-eight hours only to develop a full-blown syndrome up to 5 days following the procedure. These patients promptly responded to oral steroid therapy. An insufficient number of cases is as yet available for further comment except to speculate that in some cases increased, or repeated doses of methylprednisolone may be necessary. Of interest is the possibility that prophylactic treatment with steroids of patients about to have myelography or pneumoencephalography may modify or even eliminate the symptoms occurring during the procedure. This approach is worthy of further investigation.

#### SUMMARY

One hundred-twenty patients undergoing fractional air pneumoencephalography were divided into four groups of thirty patients each. Group I received 10 cc intrathecal instillation of normal saline following the procedure; Group II received an equal volume of methylprednisolone acetate (Depo-Medrol) and polyglycol vehicle in normal saline; Group III received an equal volume of polyglycol vehicle in normal saline; and Group IV received no injection. Subsequent examinations revealed that there was a statistically significantly decreased duration of post-pneumoencephalogram symptoms in the group receiving methylprednisolone (13.5 hours) as compared to the other groups (43–47 hours).

One hundred-twenty patients having Pantopaque myelography were studied as above. The group receiving methylprednisolone had a statistically significantly decreased incidence (10%) and duration of symptoms (5 hours) as compared to the control groups (33–40% and 25–30 hours).

It is concluded that intrathecal instillation of methylprednisolone is of significant clinical value in alleviation of symptoms following air pneumoencephalography and Pantopaque myelography.

## REFERENCES

1. Slosberg, P., and Bornstein, M.: Pneumoencephalography with Minimal Withdrawal of Cerebrospinal Fluid. *Tr. Am. Neurol. A.*, 80: 223, 1955.
2. Davidoff, L. M., and Dyke, C. M.: *The Normal Encephalogram*. Phila.: Lea & Febiger, 1951.
3. Kulick, S. A.: The Clinical Use of Intrathecal Methylprednisolone Acetate following Lumbar Puncture. *J. Mt. Sinai Hosp.*, 32: 75, 1965.
4. Kornreich, C. J.: Relief of Symptoms Following Encephalography by Combined Premedication and Use of Oxygen. *Arch. Neurol. & Psychiat.*, 60: 512, 1948.
5. Von Storch, T. J. C., and Karr, H. H.: Reduction of Pain and Other undesirable Reactions Due to Pneumoencephalography. *New England J. Med.*, 224: 755, 1941.
6. Schwab, R. S., Fine, J. and Mixter, W. J.: The Reduction of Post-encephalographic Symptoms by the Inhalation of 95% O<sub>2</sub>. *Arch. Neurol. & Psychiat.*, 37: 1271, 1937.
7. Mason, M. S., and Raaf, J.: Complications of Pantopaque Myelography. *J. Neurosurg.*, 19: 302, 1962.
8. Smith, J. K., and Ross, L.: Steroid Suppression of Meningeal Inflammation Caused by Pantopaque. *Neurology*, 9: 48, 1959.
9. Davies, F. L.: Effect of Unabsorbed Radiographic Contrast Media on the Central Nervous System. *Lancet*, 2: 747, 1956.
10. Bergman, P. Personal Communication.
11. Karlan, R. Personal Communication.

# Balloon Catheter Occlusion for Evaluation of High Pressure Patent Ductus Arteriosus

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## INTRODUCTION

The selection of patients with patent ductus arteriosus for operative intervention is determined primarily by the presence and degree of associated pulmonary hypertension. The safety and desirability of surgery in cases with normal or slightly elevated pulmonary pressure is unquestioned. In those instances where pressure in the lesser circuit exceeds systemic pressure and a constant reversal of flow exists, surgery is contraindicated (1-9).

Patients with pulmonary hypertension approaching systemic values and with phasic or only partially reversed flows, present a difficult challenge in hemodynamic assessment and suitability for surgery. Balloon catheterization, with temporary occlusion of the patent ductus in the intact chest, affords a nonoperative method of evaluation in these cases.

The use of a balloon catheter to occlude a patent ductus arteriosus was described in 1959 by Actis-Dato and Tarquini (10). This technique allows measurements of flow through and pressures on either side of a patent ductus arteriosus in the intact, non-anesthetized patient. Clinical as well as hemodynamic assessment during ductus occlusion is easily carried out.

An illustrative case is presented.

## CASE REPORT

G.B., a 21 year old female was admitted to The Mount Sinai Hospital, New York, September 10, 1962, for evaluation of a cardiac murmur first heard 5 weeks previously. She denied any symptoms related to her cardiac or pulmonary systems. Her blood pressure was 114/64, with a regular pulse of 86 per minute. The point of maximal cardiac impulse was in the fifth intercostal space one centimeter beyond the midclavicular line. There was no precordial heave, shock or thrill. The second pulmonic sound was loud and normally split. In the left second to third intercostal space there was a Grade IV/VI pansystolic murmur and an inconstantly heard Grade II/VI diastolic murmur. There was no cyanosis or clubbing. Peripheral pulses were normal.

Blood count, urinalysis and routine blood chemistries were normal. Sick cell preparation was negative. Chest x-rays revealed slight biventricular hypertrophy. Electrocardiogram was suggestive of right ventricular hypertrophy and the vector cardiogram showed possible biventricular hypertrophy.

Cardiac catheterization on September 13, 1962, revealed data consistent

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with a high pressure patent ductus arteriosus, with a resting pulmonary artery pressure of 92 systolic and a simultaneous aortic systolic pressure of 112 mm of mercury. There was no peripheral desaturation. The ratio of pulmonary to systemic blood flow was 2.4/1. Selective aortic angiography revealed a patent ductus arteriosus with pulmonic insufficiency.

Balloon catheter studies were performed October 3, 1962. A double lumen balloon tip catheter, 8½ french, with the proximal recording lumen 4 cm from



Fig. 1. Balloon catheter in place with inflated balloon occluding ductus.

the tip\* was passed via the right heart, through the patent ductus arteriosus, and into the aorta. Under fluoroscopic control the balloon was inflated with radio-opaque dye and withdrawn to occlude the ductus (Fig. 1). The systolic murmur was obliterated and the ductus remained occluded for 5 minutes with no untoward effects. The aortic pressure changed from 114/64 with a mean of 82 to 108/81 with a mean of 92. Pulmonary artery pressure fell from 118/72, mean of 89 (Fig. 2A), to 67/38, a mean of 48 (Fig. 2B). The aortic oxygen content changed from 17 to 16.3 volumes per cent, while in the pulmonary artery it fell from 15.5 to 13.3 volumes per cent.

\* (Dotter-Lukas #3, American Catheter Company).

On October 5, 1962, the patient underwent division and suture of the patent ductus arteriosus. The ductus was 2.5 cm in diameter. Operative pressures showed pulmonary artery 70/50 with a mean of 62 and brachial artery 79/55 with a mean of 62. After division of the ductus the pulmonary artery fell to 55/40 with a mean of 45 and the brachial artery rose to 90/75 with a mean of

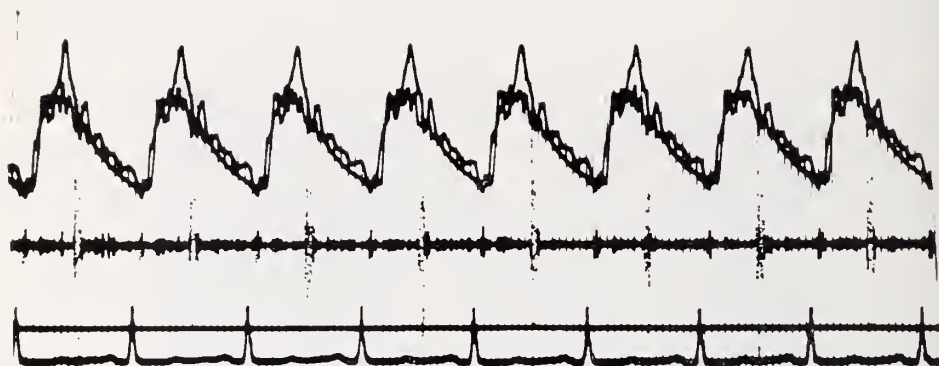


FIG. 2A. Pressure tracing prior to ductus occlusion.

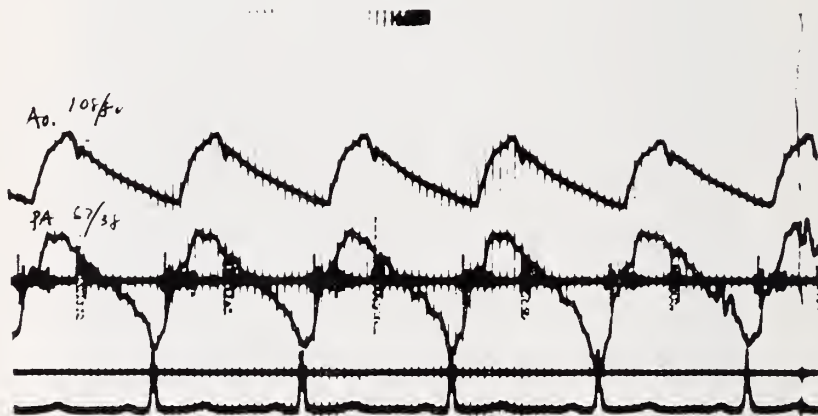


FIG. 2B. Pressure tracing during occlusion of ductus with balloon.

85 (Fig. 3). An incidental finding at surgery was hilar nodes consistent with sarcoidosis. Later, a Kveim reaction was positive.

The postoperative course was unremarkable until the eighth postoperative day when she had findings suggestive of acute appendicitis. Appendectomy was performed, at which time her appendix was normal and no intra-abdominal pathology was found to account for the clinical or laboratory findings which had led to laparotomy. The patient was discharged on October 27, 1962. There was a gradual diminution in heart size and pulmonary artery segment. The electrocardiogram showed gradual regression of right ventricular hypertrophy.



Repeat catheterization 18 months after surgery showed only minimal pulmonary artery hypertension. Right ventricular pressure was 40/0, pulmonary artery 33/17 with mean 24, and brachial artery 106/77 with mean 84.

#### DISCUSSION

Though the etiology of pulmonary hypertension in patent ductus or other extra or intracardiac left to right shunt is poorly understood, the existence of such hypertension often becomes the dominant feature in the particular lesion (1, 3-6, 11-17). The size of the shunt, previous pulmonary disease, polycythemia, persistence of fetal pulmonary vasculature and other factors have

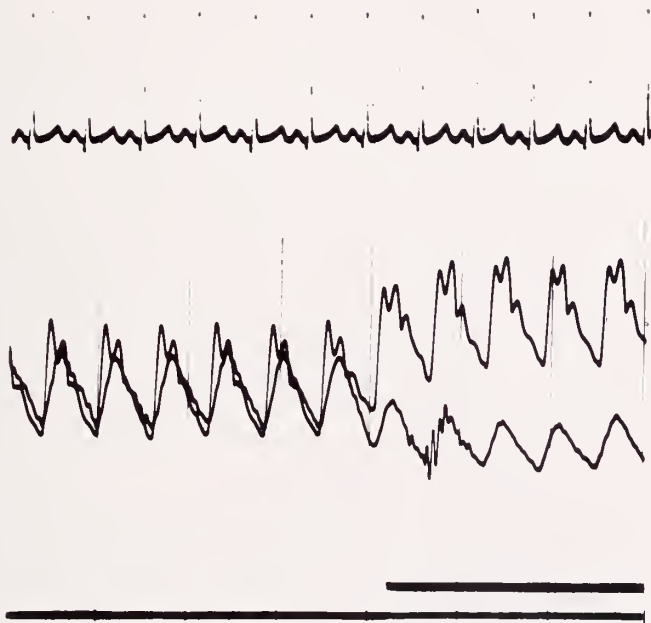


FIG. 3. Pressure tracing at the time of ductus occlusion during surgery.

been implicated as causative factors in increased pulmonary resistance, but no consistent pattern has been noted (18-28). Duration may also play a role in that the longer a shunt into the lesser circuit continues, the more enhanced is the possibility of pulmonary hypertension development (29).

In the patient with "high pressure" patent ductus, preoperative evaluation is essential because of the technical difficulties and generally brittle state of the cardiovascular system during surgery (2, 5, 30, 31). The method of balloon occlusion of the patent ductus appears to lend itself well to temporary, reversible evaluation of the hemodynamic problem.

When this procedure results in a rise in pulmonary artery pressure, a fall in systemic pressure or clinical deterioration of the patient, permanent ductus occlusion appears contraindicated. A fall in pulmonary artery pressure with

a rise in systemic pressure and well being of the patient during occlusion strongly supports operability.

If no pressure change is noted, but the patient tolerates balloon occlusion for 5 to 10 minutes without untoward symptoms, then cautious exercise tolerance testing with continuous occlusion may be tried. This latter type of patient requires further study to determine operability. It is likely that more refined surgical techniques will permit interruption of the ductus in this group of patients and will extend the value of the catheterization observations.

Regression of pulmonary hypertension has been recorded in a variety of closed left to right shunts (1, 9, 32). Braunwald, *et al.* noted that regression of pulmonary hypertension is more likely to attend the closure of an extracardiac defect than the correction of an intracardiac lesion (33).

Technically, the passage of the balloon catheter through the patent ductus is usually feasible (10, 34, 35). The procedure undoubtedly has significant risk. The prognosis for life in this group, however, is extremely poor and such risk appears acceptable rather than to subject a patient to a surgical "trial" occlusion with its attendant high morbidity and mortality.

This technique was employed in another patient (N.M.) in March, 1963. While oxygen values suggested complete ductus occlusion, no significant pressure changes were noted. The balloon was well tolerated, in the occluding position, for 10 minutes. After withdrawal of the balloon catheter, another catheter was introduced to perform angiocardiography. Atrial perforation occurred and closed pericardial drainage was required to treat pericardial tamponade. The patient recovered uneventfully. This second patient was not subjected to surgery so that follow up data are not available.

#### SUMMARY

The technique of preoperative evaluation of high pressure patent ductus arteriosus by balloon occlusion and simultaneous clinical and physiological observation is presented. This method is valuable in the selection of cases for operative interruption of a high pressure patent ductus arteriosus. Further experience with the technique coupled with surgical closure in borderline cases should serve to broaden the applicability of balloon occlusion of the patent ductus arteriosus.

#### REFERENCES

1. Campbell, M.: Patent Ductus Arteriosus: Some Notes on Prognosis and on Pulmonary Hypertension. *Brit. Heart J.*, 17: 511, 1955.
2. Crafoord, C.: Meeting of the Section of Surgery of the Royal Society of Medicine. *Brit. Med. J.*, 1: 946, 1951.
3. Daily, F. H., Genovese, P. D., and Behnke, R. H.: Patent Ductus Arteriosus with Reversal of Flow in Adults. *Ann. Int. Med.*, 56: 856, 1962.
4. Dammann, J. F., Jr., Sell, G. R.: Patent Ductus Arteriosus in the Absence of a Continuous Murmur. *Circulation*, 6: 110, 1952.
5. Ellis, F. H., Jr., Kirklin, J. W., Callahan, J. A., and Wood, E. H.: Patent Ductus Arteriosus with Pulmonary Hypertension. *J. Thoracic Surg.*, 31: 268, 1956.

6. Gerbode, F., Holman, E., Hultgren, H., Osborn, J. J., Purdy, A. P., Robinson, S. J., and Seltzer, A.: Atypical Patent Ductus. *Arch. Surg.*, 72: 850, 1956.
7. Gross, R. E., and Longino, L. A.: The Patent Ductus Arteriosus: Observations from 412 Surgically Treated Cases. *Circulation*, 3: 125, 1951.
8. Krovetz, L. J., and Warden, H. E.: Patent Ductus Arteriosus. An Analysis of 515 Surgically Proved Cases. *Dis. Chest*, 42: 46, 1962.
9. Silver, A. W., Kirklin, J. W., Ellis, F. H., Jr., and Wood, E. H.: Regression of Pulmonary Hypertension after Closure of Patent Ductus Arteriosus. *Proc. Staff Meet. Mayo Clin.*, 29: 293, 1954.
10. Actis-Dato, A., and Tarquini, A.: Evaluation of Operability in Patients with Pulmonary Hypertension by Catheterization and Occlusion of Patent Ductus Arteriosus. *Circulation*, 19: 821, 1959.
11. Hultgren, H., and Seltzer, A.: The Syndrome of Patent Ductus Arteriosus with Pulmonary Hypertension. *Circulation*, 8: 15, 1953.
12. Johnson, R. E., Werner, P., Kuschner, M., and Courmand, A.: Intermittant Reversal of Flow in a Case of Patent Ductus Arteriosus. *Circulation*, 1: 1293, 1950.
13. Jose, A. D., Ferenoz, C., Sheldon, H., and Bahnson, H. T.: Progressive Rise in Pulmonary Vascular Resistance in a Patient with a Patent Ductus Arteriosus: A Case Report. *Bull. Johns Hopkins Hosp.*, 108: 280, 1961.
14. Lukas, D. S., Ararjo, J., and Steinberg, J.: The Syndrome of Patent Ductus Arteriosus with Reversal of Flow. *Am. J. Med.*, 17: 298, 1954.
15. Meyers, G. S., Scannell, J. G., Wyman, S. M., Dimond, E. G., and Hurst, J. W.: Atypical Patent Ductus Arteriosus with Absence of the Usual Aortic-Pulmonary Pressure Gradient and of the Characteristic Murmur. *Am. Heart J.*, 41: 819, 1951.
16. Shephard, J. T., Weidman, W. H., Burke, E. C., and Wood, E. H.: Hemodynamics in Patent Ductus Arteriosus Without a Murmur. *Circulation*, 11: 404, 1955.
17. Yu, P. N., Lovejoy, F. W., Jr., Joos, H. A., Nye, R. E., and Beatty, D. C.: Studies of Pulmonary Hypertension. V. The Syndrome of Patent Ductus Arteriosus with Marked Pulmonary Hypertension. *Am. Heart J.*, 48: 544, 1954.
18. Burchell, H. B., Swan, H. C., and Wood, E. H.: Demonstration of Differential Effects on Pulmonary and Systemic Arterial Pressure by Variation in Oxygen Content of Inspired Air in Patients with Patent Ductus Arteriosus and Pulmonary Hypertension. *Circulation*, 8: 681, 1953.
19. Dammann, J. F., Jr., and Ferencz, C.: The Significance of the Pulmonary Vascular Bed in Congenital Heart Disease. III, Defects Between the Ventricles or Great Vessels in Which Both Increased Pressure and Blood Flow May Act Upon the Lungs and In Which There is a Common Ejectible Force. *Am. Heart J.*, 52: 210, 1956.
20. Douglas, J. M., Burchell, H., Edwards, J. E., Dry, T. J., and Parker, R. L.: Systemic Right Ventricle in Patent Ductus Arteriosus: Report of a Case with Obstructive Pulmonary Vascular Lesions. *Proc. Mayo Clin.*, 22: 413, 1947.
21. Evans, W., and Short, D. S.: Pulmonary Hypertension in Congenital Heart Disease. *Brit. Heart J.*, 20: 529, 1958.
22. Ferrer, M. I., and Harvey, R. M.: The Etiology of Secondary Pulmonary Hypertension. *Bull. New York Acad. Med.*, 30: 208, 1954.
23. Heath, D., and Edwards, J. E.: The Pathology of Hypertensive Pulmonary Vascular Disease. *Circulation*, 18: 533, 1958.
24. Heath, D., Helmholtz, H. F., Burchell, H. B., DuShane, J. W., and Edwards, J. E.: Graded Pulmonary Vascular Changes and Hemodynamic Findings in Cases of Atrial and Ventricular Septal Defect and Patent Ductus Arteriosus. *Circulation*, 18: 1155, 1958.
25. Heath, D., DuShane, J. W., Wood, E. H., and Edwards, J. E.: The Structure of the

- Pulmonary Trunk at Different Ages in Cases of Pulmonary Hypertension and Pulmonary Stenosis. *J. Path. & Bact.*, **77**: 443, 1959.
26. Lucas, R. V., Adams, P., Anderson, R. C., Meyne, K. G., Lillehei, C. W., and Varco, R. L.: The Natural History of the Isolated Ventricular Septal Defect. A Serial Physiologic Study. *Circulation*, **24**: 1372, 1961.
  27. Sapin, S. O.: Patent Ductus Arteriosus with Reversal of Shunt. *Tr. Am. Coll. Cardiol.*, **3**: 222, 1954.
  28. Smith, G.: Patent Ductus Arteriosus with Pulmonary Hypertension and Reversed Shunt. *Brit. Heart J.*, **16**: 233, 1954.
  29. Burchell, H. B.: Variations in the Clinical and Pathological Picture of Patent Ductus Arteriosus. *M. Clin. North America*, **32**: 911, 1948.
  30. Bothwell, T. H., Van Lingen, B., Whidborne, J., Kaye, I., McGregor, M., and Elliott, G. A.: Patent Ductus Arteriosus with Partial Reversal of Shunt. A Study of Two Cases. *Am. Heart J.*, **44**: 366, 1952.
  31. Gordon, A. J., Donoso, E., Kuhn, L. A., Ravitch, M. M., and Himmelstein, A.: Patent Ductus Arteriosus with Reversal of Flow. *New England J. Med.*, **251**: 923, 1954.
  32. Baldwin, J. S., Himmelstein, A., and Cournand, A.: Cardiac Catheterization in Congenital Heart Disease; a Clinical and Physiological Study in Infants and Children. *The Commonwealth Fund*, New York: 59, 1949.
  33. Braunwald, N. S., and Braunwald, M. D.: The Effects of Surgical Abolition of Left-to-Right Shunts on the Pulmonary Vascular Dynamics of Patients with Pulmonary Hypertension. *Circulation*, **26**: 1270, 1962.
  34. Cosh, J. A.: Patent Ductus Arteriosus with Pulmonary Hypertension. *Brit. Heart J.*, **15**: 423, 1953.
  35. Whitaker, W., Heath, D., and Brown, J. W.: Patent Ductus Arteriosus with Pulmonary Hypertension. *Brit. Heart J.*, **17**: 121, 1955.

# Gallstone Ileus

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The following report is based on three cases of gallstone ileus treated at The Mount Sinai Hospital during a recent two month period and 17 cases treated at the hospital during the 25 year period from 1938 to 1963.

Gallstone ileus is a mechanical intestinal obstruction caused by one or more stones impacted within the lumen; such stones account for about 2% of all mechanical small intestinal obstructions (1, 2, 3). Females are more often affected than males, with a generally accepted ratio of 7:1. The patients are usually in their sixties and seventies (4). The mortality rate is high, ranging from 20 to 75% in various series (5, 2, 4).

The gallstone finds its way into the small bowel following the creation of a cholecyst-enteric fistula. These fistulae begin with the formation of inflammatory adhesions between the gallbladder and adjacent organs, and subsequent erosion of a stone through the gallbladder or its main duct into the gastrointestinal tract (6). The fistula is usually between the gallbladder and the duodenum, but fistulae may develop between the gallbladder and the stomach, jejunum, ileum, colon, bronchus, pericardium or pleura. Even fistulae with the genito-urinary tract have been reported (7).

Having entered the lumen, the stone passes down the small bowel, where it may become impacted or held up by local spasm. The spasm may then relax, allowing the stone to pass down to a lower level and again cause obstruction. The usual point of obstruction is just proximal to the ilio-cecal valve (2), or elsewhere in the terminal ileum. Stones may also impact elsewhere in the gastrointestinal tract anywhere from the pylorus down to the anal canal. Those impacted at the anus can be found and removed digitally (e.g., Case 8).

Symptoms may at first be related to the inflammatory process in the gallbladder or the passage of the stone through the fistula, but this is usually not the case. More commonly, intermittent colicky abdominal pain and vomiting, as well as abdominal distention and obstipation are the presenting symptoms. Vomitus may be green or fecal, depending upon the level of the obstruction. Symptoms may be intermittent as the stone becomes lodged at one level causing symptoms of obstruction, and then passes further along the bowel with temporary relief of the obstruction. When first seen, the patient's symptoms may be vague as in Case 1 or may immediately suggest the diagnosis (Case 2).

The physical signs are those of intestinal obstruction. The patient is usually very ill with dry and furred tongue and some abdominal distention, though this may not be apparent, as most are obese. Visible peristalsis is

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rarely present. Borborygmi may be increased in the earlier stages, though the abdomen may be silent as a result of inflammation or early gangrene at the site of impaction. When there is local tenderness in the region of the gallbladder this is a valuable sign and may be the first indication of the diagnosis.

Clinical features, on the whole, contribute little to the diagnosis and nowadays, if the diagnosis is made preoperatively, it is nearly always the x-ray findings which have led to it.



FIG. 1. Case 1—Flat film of the abdomen. Note air in the biliary tree.

The plain film of the abdomen is of great value in establishing the diagnosis of gallstone ileus (8). The diagnostic picture is of air in the biliary tree associated with distended loops of small bowel (Fig. 1, Fig. 4). At times the gallstone may actually be demonstrated within the intestine (9), or it may change its position from the gallbladder to a new location (Case 3). Cholecyst-enteric fistulae may be demonstrated with radiopaque material, but this is usually not necessary.

Treatment is surgical. Several hours of fluid and electrolyte replacement may be necessary in the preoperative period, and gastrointestinal intubation

may be helpful during this waiting period, but prolonged delay in operative intervention is dangerous.

Surgery is aimed at relief of the obstruction. The segment of the bowel in which the stone lies impacted, is usually edematous and inflamed (Fig. 2). The stone is therefore "milked" proximally into a relatively normal segment of bowel and removed through an enterotomy.

This is the classic treatment recommended in those cases where the stone can be shifted. There are, however, occasions when it can not be disimpacted. For these it has been recommended (9) that an enterotomy be done distal to



FIG. 2. Case I—Small bowel: stone can be seen through the thinned-out wall of the ileum.

the stone and the stone crushed by means of an instrument passed through this. However, the maneuver may be dangerous and even when the stone can be grasped and crushed, serious damage can be done to the already devitalized mucosa (4). In cases where ulceration or gangrene has occurred at the site of impaction, resection of the affected segment with end-to-end anastomosis (4) or exteriorization of the bowel, in a patient who is too ill to withstand resection (3), is recommended.

Stones may be multiple, and careful inspection of the stone is required for the presence of a facet which indicates that other stones may be present in the bowel, gallbladder or both. A search may show another stone in the gastrointestinal tract, either loose or impacted. The gallbladder is usually found to be obscured in an inflammatory mass. Rarely is the patient's condition good enough for cholecystectomy and exploration of the ducts. It is therefore usu-

ally necessary to leave the gallbladder and reoperate when the patient has fully recovered from the intestinal obstruction. It is then sometimes noted that the fistula has closed spontaneously, or at least shrunk down considerably. If the gallbladder is not operated upon, new stones will almost certainly form.

#### CASE REPORTS

##### *Case 1, A. O'N.*

A previously well 60 year old woman was admitted with a 5 day history of anorexia and nausea. Two days before admission, she began to vomit inter-



FIG. 3. Case I—Removal of stone through enterotomy after milking it proximally into normal bowel.

mittently and became obstipated. The day before admission, she began to have dull, almost constant left lower quadrant pain and her temperature rose to 102 degrees. A history of "fullness" and "heartburn" following the ingestion of fatty foods was obtained.

Examination of the abdomen revealed moderate tenderness in the left lower quadrant, localized guarding and hypoaëctive bowel sounds. Her abdomen was not distended. The blood count was normal. The working diagnosis was diverticulitis of a mild degree. Intravenous fluid and tetracycline were given, and the patient appeared to be comfortable. The following day she still had minimal left lower quadrant abdominal signs. She remained afebrile, but her white count had risen to 12,600. Bilirubin was 3.2 mgm%, and alkaline phosphatase was normal. Plain films of the abdomen revealed gas and fluid in

several loops of proximal small intestine, which appeared to be considerably dilated. Also noted was a small amount of streaky gas in the biliary tree (Fig. 1). An x-ray examination with gastrografin swallow was performed and this demonstrated a cholecystoduodenal fistula as well as a cholecysto-colic fistula (to the hepatic flexure). During the course of the examination, the patient's abdomen became somewhat distended, and she began to vomit; she was operated upon forthwith. The major portion of the small bowel was collapsed. Upon tracing the collapsed bowel proximally, a hard, spherical object was encountered within the lumen of the bowel which lay in the left lower quadrant. Immediately proximal to this, the bowel was dilated, edematous, inflamed, and covered by a shaggy fibrinous exudate. The point of obstruction was  $3\frac{1}{2}$  feet from the ligament of Treitz. A firm 10 cm mass covered by adherent omentum was palpated in the area of the gallbladder. The stone was "milked" proximally into an area of relatively normal bowel (Fig. 2) and was removed through a small enterotomy (Fig. 3). The stone was smooth, oval, dark green in color and measured 4 cm in length. The patient's post-operative course was uneventful and she was discharged on the twelfth post-operative day, and has been well since then.

*Comment.* Symptoms in this case were at first vague and suggested colonic disease. Later, signs and symptoms of small bowel obstruction developed. Diagnosis was made on x-ray examination. Two unusual features were the presence of two fistulae from the gallbladder and the high level of obstruction (jejunum) caused by the stone.

#### *Case 2, W.L.*

A 61 year old female entered The Mount Sinai Hospital with a 3 day history of abdominal cramps and 2 days of abdominal distention, vomiting and obstipation. She had had no previous surgery, but was hospitalized in 1958 because of biliary colic. She was an obese, ill, white female with temperature of 103 degrees, vomiting brown fecal smelling material. Films of the abdomen demonstrated many dilated small bowel loops containing air fluid levels and air in the biliary tree (Fig. 4). She was given intravenous electrolyte solutions, antibiotics and rectal aspirin. A Cantor tube was passed, and four hours after admission she was explored. Many loops of moderate to markedly dilated small bowel were encountered. Several collapsed loops were seen in the right lower quadrant (Fig. 5). The collapsed terminal ileum was traced proximally until a gallstone measuring 3 cm in diameter was located 18" from the ileocecal valve. The bowel in the area of the stone was edematous and had a fibrinous exudate on its surface. The stone was removed in a manner similar to that used in the first case. The stone was yellowish, firm, spherical and non-facetted. A firm mass was felt in the right upper quadrant of the abdominal cavity. The patient ran a febrile course for five days, after which her temperature gradually returned to normal. She was discharged on the fifteenth postoperative day.

*Comment.* This case presented as an obvious low small bowel obstruction. The diagnosis of gallstone ileus was made without x-rays because of the



patient's history of gallbladder disease, the fact that she had had no prior surgery and probably most important, because the first case had been seen only 6 weeks earlier.

The stone was found in its most common location, the terminal portion of the ileum.



FIG. 4. Case II—Upright film of abdomen showing dilated loops of small bowel, fluid levels, and air in the biliary tree.

#### *Case 3, R. R.*

This 82 year old white female was admitted to The Mount Sinai Hospital with a 24 hour history of crampy abdominal pain. One year prior to admission, she was operated upon at another hospital for pyloric obstruction. A large inflammatory mass was found which was causing extreme pressure on the pyloroantral region of the stomach. It was presumed to be a carcinoma of the gallbladder, and a gastro-jejunostomy was done. She was well until the day prior to admission when she developed abdominal pain, obstipation, nausea and vomiting. She was afebrile. Examination of the abdomen revealed diffuse tenderness and diminished bowel sounds. White count was 16,000. An obstructive x-ray series demonstrated some air in the biliary tree, and a large cal-



cification which was presumed to be in the gallbladder, but no evidence of intestinal obstruction (Fig. 6). Intravenous fluids were administered. The patient continued to complain of vague abdominal pain, mainly in the left lower quadrant. She remained afebrile. On the fourth hospital day, she began to vomit and her abdomen became distended. Repeat films of the abdomen revealed dilated small bowel loops, and the previously noted right upper quadrant calcification had disappeared. Laparotomy was performed and two gallstones, one 4 cm in diameter and the second 2½ cm were found in the terminal ileum.



Fig. 5. Case II—Small bowel: dilated and collapsed bowel proximal and distal to the obstruction.

The patient's subsequent course was uneventful and she was discharged on the sixteenth postoperative day.

*Comment.* The interesting feature in this case is the presence of multiple stones. At the time of the first film, one stone had already passed into the bowel, causing the patient's symptoms and accounting for the presence of both air and a stone in the biliary system. Further symptoms were caused after the passage of the second stone, and the complete obstruction which followed.

#### REVIEW OF CASES: 1938-1963

During the 25 year period from 1938 to 1963, 20 patients with gallstone ileus were admitted to The Mount Sinai Hospital. These cases are summarized in Chart I.

*Age.* The average age was 68.3 years, the youngest patient being 53 and the oldest 86 years old. The majority of cases fell into the 60-69 year age group.

*Sex.* There were 16 females and 4 males—a ratio of 4:1. Sixteen patients had known gallstones or a history of gallbladder disease.

*Location of fistulae and stones.* The exact location of a fistula was established either by post mortem examination or by roentgenographic contrast studies in 7 cases. One cholecystogastric fistula and 6 cholecystoduodenal



FIG. 6. Case III—Plain film of the abdomen. Note stone in the gall bladder and air in the biliary tree. No evidence of obstruction.

fistulae were demonstrated. Of the latter, one was associated with a cholecystocolonic fistula (hepatic flexure) and one was a double fistula to the duodenum.

The obstruction was usually caused by a single large stone, but multiple stones in the same location were found in two patients. (In a case not included in this series, two stones were found in different locations simultaneously. One was impacted in the pylorus and a second in the jejunum. A cholecyst-gastric fistula was present.)

The majority of stones became impacted in the ileum; 11 in the lower por-

tion and 3 in the upper ileum. Of those stones recovered from the lower ileum, most were not impacted at the ileocecal valve, but were a distance of from one to three feet from it. Two stones lodged in the jejunum, one at the pylorus (vomited spontaneously) and two stones had to be removed from the rectum. Only one stone was spontaneously passed per rectum.

*Treatment.* Sixteen of the twenty cases underwent surgery for relief of intestinal obstruction, and five were treated nonoperatively. One patient (Case 9) had recurrent episodes of obstruction. The first was relieved spontaneously when she vomited a large gallstone. The second obstruction required a laparotomy. This accounts for the apparent discrepancy in the total number of cases.

Since gallstone ileus is usually considered a surgical problem, it is of interest to note that six cases were treated non-operatively, and the results that were obtained were as follows: One patient vomited a large gallstone and relieved the obstruction spontaneously. Three patients (Cases 3, 10 and 12) were not operated upon because of their "extremely poor general condition." One had been ill for a week prior to hospitalization and died within 24 hours of admission. The second patient had been obstructed "for several days" prior to admission. Her diagnosis was never entirely clear. Initial conservative management using intravenous fluids and nasogastric suction was successful, but the patient's condition soon deteriorated and she died. Post mortem examination revealed an obstructing gallstone in the lower ileum, and pulmonary emboli.

The third patient had been vomiting for 5 days prior to admission and was treated at first with nasogastric suction and intravenous fluids. Her general condition improved and she passed a large gallstone by rectum. She again entered the hospital six months later with low grade intestinal obstruction. She was again treated conservatively, but this time failed to improve and was explored. At surgery, she was found to have an infiltrating adenocarcinoma of the gallbladder with invasion of the root of the small bowel mesentery producing mesenteric vascular occlusion and gangrene of the small intestine. She died two days later. The original cholecystoduodenal fistula was demonstrated at the post mortem examination.

One patient (Case 8) was in good general condition, but it was elected by her physician to treat her non-operatively. X-rays showed small bowel obstruction and the absence of a previously demonstrated gallstone from the right upper quadrant. Several days later, films showed large and small bowel obstructions and a gallstone in the rectum. This was removed manually and the patient rapidly recovered.

In the majority of operated cases, a simple enterotomy and removal of the stone was performed. In one case (No. 2), the enterotomy was converted into a Witzel type enterostomy for decompression and feeding. One patient was originally seen in another hospital because of abdominal cramps and vomiting. After two weeks of treatment with long tubes, an ascending colon colostomy was performed. The patient was seen at The Mount Sinai Hospital five

CHART I  
*Gallstone Illness*

Case no.	Sex	Age	Year	History & physical examination	X-ray	Fistula location	Stones			Time from admission to surgery	Days in hosp.	Cause of death
							No.	Size	Location			
1	F	62	1938	10 yr. history of chronic GB disease. Acute cholecystitis 5 mos. PTA RUQ pain and vomiting—5 days. PE: Dehydration peritonitis. Palpable gall bladder.		Cholecysto-duodenal	1	3 cm	40 cm from ileocecal valve	12 hrs.	1	Bronchopneumonia (P.M.)
2	F	64	1939	10 yr. history of gall bladder disease. Abdominal pain and constipation—4 days. PE: Acutely ill, peritonitis.			1	?	Proximal ileum	Within 24 hrs.	11	"Paralytic ileus" (No P.M.)
3	F	67	1940	1 yr. history of gall bladder disease. Abdominal pain and vomiting 1 month. Obstruction—several days. PE: Cachectic; dehydrated.	Distended small bowel, some gas in colon	Cholecysto-duodenal (1st portion)	4	2.5 to 3.5 cm.	Proximal ileum		30	Bronchopneumonia (P.M.) 2 stones eroded into peritoneal cavity.
4	M	55	1940	Episodes of crampy upper abdominal pain, nausea and vomiting. PE: Abdominal distention.	Dilated small bowel		1	"Plum"	75 cm. from ileocecal valve Rectum	3 days	14	
5	F	69	1940	Long history of gall bladder disease. Intestinal obstruction—5 mos. PTA Had ascending colon colostomy. Crampy abdominal pain—4 mos. PE: Stony hard mass in rectum.	Nonvisualizing gall bladder		1	3.5 cm.			8	
6	F	76	1943	Obstipation—3 days. Vomiting 2 days. PE: Abdominal distention—generalized tenderness.	Small bowel obstruction	Double cholecysto-duodenal	1	"Plum"	Proximal ileum	Within 24 hours	4	Cardiac failure (P.M.)

7	F	62	1945	20 yr. history of recurrent episodes of RUQ pain. Vomiting—11 days. Fever—2 days. PE: T. 102° Generalized abdominal tenderness.	Small bowel obstruction	Cholecysto-gastric	1	"Pigeon Egg,"	Hem	9 days	23	
8	M	68	1945	Crampy abdominal pain—3 days—Distention and obstipation—2 days. PE: Abdominal distention and tenderness.	Old film—gallstone. New film—no gallstone in RUQ. Small bowel obstruction. Stone in rectum		1	?	Rectum		6	
9	F	53	1947	Acute cholecystitis, 1 yr. PTA. Nausea and vomiting—3 days. Vomited gallstone. PE: T101° RLQ tenderness.	3.5 cm. Laminated RUQ concretion		1	?	Stomach		13	
9A	F	53	1947	Not well since discharge 6 weeks PTA. Vomiting, LLQ pain, obstipation—2 days. PE: Abdomen soft, diffusely tender.	Small bowel distention, stone in mid abdomen, no stone in RUQ		1	3.5 cm.	Jejunum	Within 24 hours	10	
10	M	83	1952	Acute cholecystitis 1 year PTA. Nausea and vomiting and RUQ pain—1 week. PE: T 102°. Stereopous, dehydrated.	Dilated small bowel.	Cholecysto-duodenal	1	?	Distal ileum		24	"Gallstone ileus" pulmonary embolus (P.M.)
11	F	68	1953	Long history of gallstones. RUQ pain—3 days. Diffuse pain and obstipation—2 days. PE: Abdominal distention.	Stone in small bowel		1	5 cm.	Proximal to ileocecal valve	Within 24 hours.	14	
12	F	86	1956	Long history of gallbladder disease. Vomiting and constipation—5 days. PE: Dehydrated, abdominal distention and tenderness	Dilated small bowel, ring shadow in RLQ	Cholecysto-duodenal (2nd portion)	1	?	Passed per rectum		14	Readmitted 6 mos. later and explored—had adenocarcinoma of gallbladder



CHART I—Continued

Case no.	Sex	Age	Year	History & physical examination	X-ray	Fistula location	Stones			Time from admission to surgery	Days in hosp.	Cause of death
							No.	Size	Location			
13	F	72	1957	Cholecystitis 6 yrs. PTA. Nausea, vomiting, abdominal pain, constipation—4 days. PE: RUQ tenderness. Moderate distention.	Dilated small bowel, air in biliary tree, stone in RLQ		1	"Plum"	90 cm from ileocecal valve	Within 24 hours	28	Myocardial infarction (No P.M.)
14	F	64	1958	Long history of gallbladder disease. Nausea, vomiting, crampy abdominal pain, obstipation—1 day. PE: slight abdominal distention.	Small bowel obstruction		1	?	?	5 days	32	
15	F	75	1959	15 year history of gallstones. Vomiting—5 days. Constipation—4 days. PE: RUQ tenderness. Abdominal distention.	Distended small bowel. Air in biliary tree. Stone in RLQ.		1	3 cm.	15 cm. from ileocecal valve	Within 24 hours	11	
16	M	70	1961	Acute cholecystitis 2 years PTA. Abdominal pain and vomiting—3 days. Obstipation—2 days. PE: Abdominal distention, diffuse tenderness.	Small bowel obstruction. Air in biliary tree. Stone in RLQ.		1	1.5 × 3 cm.	Distal ileum	Within 24 hours.	39	
17	F	69	1961	Nausea and vomiting—3 days. PE: High-pitched bowel sounds. Abdominal distention.	Small bowel obstruction. Stone in RLQ.		1	2 × 3 cm.	5 cm. from ileocecal valve.	2 days	37	
18	F	82	1963	Had gastroenterostomy 1 year PTA to bypass a large mass obstructing the pylorus (probably gallbladder). Cramps, nausea, vomiting—1 day. PE: Diffuse abdominal tenderness.	1) Air in biliary tree. Calcification in gallbladder 2) No stone in G.B. Small bowel obstruction. Stone in pelvis.		2	2.5 × 4 cm.	Terminal ileum.	4 days	19	

19	F	60	1963	Anorexia and nausea—5 days. Vomiting—2 days. Abdominal pain (LLQ)—1 day. PE: LLQ tenderness.	Small bowel obstruction, air in biliary tree. Fistulae.	Cholecystoduodenal and cholecystocolic	1	4 cm.	100 cm. from ligament of treitz	Within 24 hours	14
20	F	61	1963	5 year history of gallbladder disease. Crampy abdominal pain—3 days. Distention, vomiting, obstipation, fever—2 days; PE: T 103°—fecal vomitus. Abdominal distention and tenderness.	Small bowel obstruction, air in biliary tree.		1	3 cm.	45 cm. from ileocecal valve	4 hours	15

months later because of a stony hard mass in the rectum. The mass was removed manually and proved to be a  $1\frac{1}{2}$ " laminated gallstone.

Three of fourteen cases which survived more than four days had wound infections.

*Mortality.* There were six deaths in the series, an overall mortality of 30%. Operative mortality was 25%. The two patients who died during conservative therapy have already been discussed. The four postoperative mortalities will be examined in more detail.

One patient was doing well after removal of a gallstone from her ileum. However, she had several myocardial infarctions during the second and third postoperative week and died of her heart disease. The three remaining cases were all seen late in the course of their disease and were in poor condition when they entered the hospital. All were operated upon within 24 hours of admission. One patient died 7 hours postoperatively. Death was found on post mortem examination to be due to bronchopneumonia.

The second patient died on the fourth postoperative day due to cardiac failure. The third patient had peritonitis at the time of surgery from which he never recovered.

It is interesting to note that the majority of deaths occurred during the early years of this 25 year survey and that several of these had evidence of obstruction for many days prior to admission to the hospital. There were no deaths in the last seven cases occurring since 1958.

#### DISCUSSION

The high mortality generally associated with gallstone ileus is largely due to the delay which takes place between the onset of symptoms and the establishment of the correct diagnosis. In some cases it is due to an even longer delay after the diagnosis has been made. Early operative intervention is the treatment of choice in this disease, and delay in surgery for significant periods of time in the hope that the stone will pass spontaneously or in the usually vain attempt at long tube decompression is to be condemned.

An awareness of the existence of the disease, the value of a careful history, and the search for x-ray evidence of air in the biliary tree are all necessary to encourage early diagnosis and operation.

#### SUMMARY

1. A general discussion of the incidence, pathology, symptomatology and diagnosis of gallstone ileus is presented.
2. Three recent cases of gallstone ileus are presented in detail.
3. An additional 17 cases are summarized and analyzed.
4. The importance of early diagnosis and surgery is stressed.

#### REFERENCES

1. Barnard, H. L.: Intestinal Obstruction due to Gallstones. *Ann. Surg.*, 36: 61, 1902.
2. Deckoff, S. L.: Gallstone Ileus. *Ann. Surg.*, 142(1): 52, 1955.

3. Wakely, C. P. G., and Willway, F. W.: Intestinal Obstruction by Gallstones. *Brit. J. Surg.*, 23: 377, 1935.
4. Jenkins, H. P., and Evans, R., and Koller, W.: Gallstone Ileus, *Surg. Clin. N. Amer.*, 41(1): 71, 1961.
5. Brockis, J. G., and Gilbert, M. C.: Intestinal Obstruction by Gallstones. *Brit. J. Surg.*, 44: 461, 1957.
6. Ackerman, L. V. and Butcher, H. R., Jr.: *Surgical Pathology*, 2nd ed., St. Louis: C. V. Mosby Co., 1959.
7. Powers, J. H.: Acute Intestinal Obstructions due to Impacted Gallstones. *Surg. Gynec. & Obst.*, 47: 417, 1928.
8. Rigler, L. G., et al.: Gallstone Obstruction, Pathogenesis and Roentgen Manifestations. *J.A.M.A.*, 117: 1753, 1941.
9. Lee, M.: Intestinal Obstruction by Gallstones. *Brit. Med. J.*, 1: 555, 1945.
10. Shepherd, J. A.: *Surgery of the Acute Abdomen*. Baltimore: Williams & Wilkins Co., 1961.

# Phenformin, Diabetic Control, and Body Weight

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Addition of D.B.I. improved the control in 63% of patients previously poorly controlled with Orinase or insulin alone. A relationship was noted in that greater dosage was associated with greater reduction and that longer duration of treatment also influenced the final weight.

This paper is a retrospective study of the use of phenformin (D.B.I.) in the management of the diabetic state. The influence of phenformin on body weight, its relationship to control of the diabetic state, and the interrelationship of these variables have been evaluated and form the major basis for this report. A theory of phenformin action is proposed and indirect evidence for its validity is presented.

## MATERIALS AND METHODS

The population under investigation consisted of patients in the Diabetes Clinics of the Elmhurst and Greenpoint Hospital Divisions of The Mount Sinai Hospital of New York. The clinics consisted of a total of 627 patients, 46% Caucasian, 30% Puerto Rican, and 24% Negro, all indigent. The patients were seen by the same three internists at regular intervals for a period of six months to two years. On each clinic visit the patient was weighed. Urine samples (mid-afternoon, bedtime, and before breakfast) were examined for sugar by the Clinitest method. In addition, all patients received a diet designed to limit an excess amount of carbohydrate and were urged to maintain or reach an ideal weight. Blood sugars were determined by the Hoffman method (1) at appropriate intervals in the Greenpoint laboratory.

The following data were obtained for each of the patients in the study: age, sex, population group, duration of diabetes, blood pressure, type of therapy, duration of therapy and blood sugar. Diabetic control was graded by Clinitest results:  $n = 0$ , trace =  $\frac{1}{2}$ ,  $1+ = 1$ ,  $2+ = 2$ , etc. The results of three visits prior to the addition of phenformin were computed and were later compared to those of visits immediately preceding the final collection of the data. Reduction by one half or more of the earlier tests scores constituted a good response. Serum cholesterol and triglycerides were obtained and are presented in a subsequent paper.

A total of 72 subjects, 14 males and 58 females, were investigated. Thirty-eight per cent were Caucasian, 24% were Negro, and 38% were Puerto Rican. This distribution was similar to that of the clinic (Table I). There were 4 subjects ages 20-34, 26 subjects ages 35-59, and 32 subjects over the age of 60.

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## RESULTS

*Effectiveness of phenformin.* Success as judged by a reduction in the initial composite urine sugar score by more than 50% was achieved in 44% of the patients taking phenformin and insulin, and 71% of the subjects taking phenformin and tolbutamide. This combination therapy was successful in 38 of 60 patients, or 63%. The number of subjects taking phenformin alone was too small for evaluation. It should be stated that phenformin was given only to patients not adequately controlled by insulin or tolbutamide alone (Table II).

*Age.* The addition of phenformin to either insulin or tolbutamide improved diabetic control in 68% of the subjects 35–59 years of age, and in 65% of subjects over the age of 60. One of four patients under the age of 34 benefited from the combination therapy (Table III).

*Sex.* The combination of phenformin and tolbutamide was successfully employed in 88% of male subjects and in 68% of female subjects. The combination of phenformin and insulin was successfully utilized in 61% of female subjects. The male phenformin and insulin subgroup was too small to evaluate. Taken together, the two combination therapies were successful in 54% of male subjects and in 66% of female subjects (Table II).

*Population group.* Seventy per cent of Caucasian, 54% of Negro and 62% of Puerto Rican subjects responded favorably (Table III).

*Weight.* Weight loss of more than 5 pounds or a gain of more than 5 pounds was considered significant. For the purpose of this study, subjects who fell between these limits were arbitrarily considered to have had no change in weight. Thirty-seven per cent of subjects receiving phenformin and insulin, 35% on phenformin and tolbutamide and 37.5% on phenformin alone lost more than five pounds after the addition of phenformin to the therapeutic program. Thirty-one and one-half per cent, 9%, and 50% respectively of these groups gained more than 5 pounds. No change was noted in 31.5% of the phenformin and insulin group, 56% of those subjects on tolbutamide and phenformin, and 12.5% of those on phenformin alone. Weight loss in 26 subjects ranged from 5 to 33 pounds with a median loss of 11 pounds. It was of interest to compare dose relationship weight loss in patients losing more than 10 pounds. In the small group taking 50 mg of phenformin only one out of four patients lost more than 10 pounds. In the patients receiving 100 mg of phenformin, six patients in a group of eleven patients lost more than ten pounds with five losing sixteen to twenty-one plus pounds. This greater loss of weight with higher dosage of phenformin was also seen in the 150 mg group where five out of 11 patients lost eleven or more pounds (Table IV).

*Duration of treatment.* Of patients taking phenformin for 6 to 12 months and losing more than 5 pounds, only three out of ten lost 11 or more pounds. When phenformin had been taken for 13 to 25 months, nine patients out of a comparable group of sixteen lost eleven or more pounds. Six of these patients lost 16 or more pounds (Table IV).

*Relationship of control to weight gain or weight loss.* Eighteen per cent of improved control subjects receiving phenformin alone or in combination therapy

gained more than 5 pounds, while 29% lost more than 5 pounds. In the unimproved group 9% gained more than 5 pounds and 36% lost more than 5 pounds. Fifty-three per cent of improved control subjects and 55% of unimproved control subjects remained at the same weight (Table IV).

*Dose relationship.* Twenty-six per cent of patients receiving 50 mg, 10% of those receiving 100 mg, and 25% of those receiving 150 mg gained more than 5 pounds (Table IV). Twenty-one per cent of subjects receiving 50 mg, 40% receiving 100 mg, and 40% receiving 150 mg per day lost more than 5 pounds and were further evaluated to see if the weight loss was due to high phenformin dosage or to poor control. Degree of control was known in 20 of these 25 subjects. Thirty-three per cent of the improved group and 45.5% of the unimproved group lost weight. Weight gain of more than 5 pounds was more frequent in the improved group, 33.3% as compared with 9% (Table IV).

An evaluation was made of the interrelationship of age, sex, duration of diabetes, population group, and body weight to weight gain or weight loss in phenformin treated subjects. Ideal body weight was estimated by the formula 110 lbs.  $\pm$  5 lbs. for every additional inch over or under 5 feet of height for men, and 100 lbs.  $\pm$  5 lbs. for women. Per cent overweight was calculated as follows:  $\text{present weight} / \text{ideal weight} \times 100$ .

Subjects above the age of 55 with diabetes of relatively short duration (less than 5 years) were most likely to lose weight although other groups also benefited. There was essentially no difference in weight loss among the population groups.

There was a greater rate of weight reduction in the group that weighed less than 50% above their ideal weight than in those who were either under weight or massively obese (Table V).

#### DISCUSSION

Our results show that phenformin in poorly controlled patients on insulin or tolbutamide resulted in improved diabetic control in 63% of the subjects. Improvement was not related to age, sex, population group, positive family history of diabetes or diastolic blood pressure. The percentage of success was similar to that of other reports in the literature (2-5). There was a loss of more than five pounds in 37% of 8 patients on phenformin alone. Absolute weight loss ranged from 5 to 33 pounds with a median loss of 11 pounds. A higher dosage of phenformin was associated with a higher percentage of patients losing weight. There was a loss of more than 5 pounds in 40% of patients receiving 100 mg of phenformin per day and 40% receiving 150 mg per day. By comparison there was weight loss of more than 5 pounds in only 21% receiving 50 mg per day. This trend of greater effectiveness of 100 mg or 150 mg as opposed to 50 mg of phenformin was seen again in the patients losing 11 or more pounds. Only 25% of the 50 mg group losing more than five pounds lost this much weight. Even more significant is that in the total of 19 patients receiving 50 mg of phenformin only one lost 11 or more pounds. In subjects taking higher dosages (100 mg or 150 mg) however, and falling in the group

that lost more than 5 pounds, 50% lost more than 10 pounds. If the group could be studied for a longer period of time, this might have been more striking since, in patients taking phenformin for 13-25 months instead of 6-12 months, 56% lost 11 or more pounds as opposed to 30%.

The relationship of weight loss to diabetic control was carefully evaluated since good control is generally associated with maintenance of body weight and poor control is often associated with weight loss. It is a common clinical observation however that many people with poor control will nevertheless gain weight. This is due to the fact that their caloric intake is greater than their body expenditure in addition to the glucose lost in the urine.

Poor control did not explain the weight loss. There was a loss of more than 5 pounds in 36% of patients under poor control but there was also this weight loss in 29% of those whose control was good. In addition, 9% of the unimproved group gained more than 5 pounds. The greater weight loss in the unimproved group may be explained at least in part by the fact that they received a higher dosage of phenformin (Table IV). Of 20 patients treated with 150 mg of phenformin per day, 9 had improved diabetic control and 11 experienced no improvement. Thirty-three per cent of this group with improved control lost more than five pounds. Forty-five and five tenths per cent of the unimproved group on 150 mg lost the same amount. This suggests that of the two factors operative, dosage of phenformin and control of the diabetic state, the former is the more important. This was retrospectively studied; therefore, no particular group can be said to be influenced by the bias of the investigator. Significant weight loss (5 pounds or more) occurred most frequently in subjects over the age of 60 with diabetes of less than five years duration, although subjects of similar age with diabetes of longer duration and younger subjects with diabetes of both short and long duration also lost weight. The sex or population group of the subject did not appear to influence weight loss. Subjects exceeding their ideal body weight by less than 50% tended to lose weight more frequently than did the markedly obese or underweight subjects.

The claim has been made by others that phenformin can facilitate weight reduction in the diabetic patient. Review of the literature reveals that Patel and Stowers, using phenformin, claimed failure to produce weight loss in obese diabetics in only 7 of 160 patients (6). This result was achieved in the face of better control of the blood sugar. The weight loss was attributed to anorexia although the average dose of phenformin was 75 mg, an amount not associated with anorexia in our study or in the majority of clinical reports.

Moss, *et al.* with a measured diabetic diet and with less than 15% of 44 adult patients affected by anorexia, nausea, diarrhea, or metallic taste, stated that 3 patients gained weight, 12 remained stationary, and 29 showed a consistent weight loss while taking phenformin. In this study there was excellent, fair, and poor control in all three groups (7).

Weller, *et al.* studied 46 obese patients receiving phenformin, 85% of whom were satisfactorily controlled. He noted a gradual reduction in weight toward, but not significantly below, estimated normal weights in many of the cases. The exact number was not given (8).

Radding, *et al.* observed that of 10 patients receiving sulfonylureas, 5 gained and 5 lost weight; of 5 patients treated with insulin, 2 gained and 3 lost; in 9 patients receiving phenformin, 6 gained and 3 lost weight (9).

A number of factors influence weight loss, among them psychological, genetic, specific caloric intake and activity. One must also postulate the additional mechanism of phenformin's action in producing weight loss in these cases. To begin with, it is important to know what metabolic process in the normal subject is associated with weight gain and then find out where phenformin enters the picture. There are two main metabolic pathways of carbohydrate metabolism in the cell. The first, the Embden-Mayerhof, is "anaerobic" and liberates all six carbon atoms of glucose as  $\text{CO}_2$ . The main oxidative coenzyme in this pathway is CoI, or DPN. The other takes place in the cytoplasm rather than the mitochondria and is the oxidative hexose monophosphate shunt. The main enzyme in the latter pathway is coenzyme II (TPN, NADP). In the liver up to half the carbohydrate metabolism may proceed through this pathway, although the shunt is important for the reductive synthesis of long chain fatty acids, gluconeogenesis from aminoacids, biosynthesis of cholesterol, steroids, purines, and aminoacids (10).

Briefly stated, the E-M pathway with coenzyme I acting as the main hydrogen carrier leads to the oxidation of hydrogen with  $\text{CO}_2$  and  $\text{H}_2\text{O}$  as products. This is conducive to weight loss. The HMS pathway with coenzyme II (TPN  $\text{H}_2$ ) as the transport link leads to the storage of hydrogen as fatty acids and tryglycerides and consequent weight gain.

One can propose a theory of surplus, that is, too much insulin or too much glucose acting as a stimulus for increased insulin production can stimulate the pentose-phosphate shunt. Siperstein has stated that dietary glucose in excess of that required for immediate energy could be preferentially directed into the pentose-phosphate route under the influence of insulin resulting in increased  $\text{CoII.H}_2$  with stimulation of lipogenesis and storage of glucose as fat. This could be under the influence of a transhydrogenase. In conditions of carbohydrate deprivation the E-M pathway is operative and the rate of weight loss is increased (11). This could be the explanation for the effect of "gorging" rather than isocaloric "nibbling" on lipogenesis in rats (12). Gordon's study demonstrated that when humans as well as animals ate large infrequent meals, energy was stored in the body as fat. Small frequent meals (nibbling) discouraged it (13). It was also demonstrated by investigators in Prague that excessive weight, increased serum-cholesterol, and diminished glucose tolerance were significantly more common among those taking 3 meals or less than those taking more than 3 meals (14).

Not only the spacing of feedings but the type of food consumed influences the choice of pathway utilized. Keys has demonstrated that substitution of sugar by isocaloric amounts of more slowly absorbed vegetable carbohydrates can lower serum cholesterol significantly (15). This again implies E-M activity.

In laboratory experience it is also evident: Winegrad and Renold dem-



onstrated increases in HMS activity and a corresponding increase in lipogenesis in adipose tissue exposed to insulin (16). Glick also demonstrated significant increased activities of the dehydrogenases of the shunt pathway in animals treated with insulin (17). The amount of insulin might have been important in their findings, for the fact that excess insulin might be at fault is seen in patients with islet cell adenomas. These patients frequently gain a great deal of weight. This is ascribed to the hypoglycemic attacks requiring the patients to eat more food. Less well known is that in tumor slices of islet cell adenomas more  $^{14}\text{CO}_2$  is derived from glucose 1-C than from glucose 6-C, implicating the HMS pathway as the one in operation in this condition (18).

It is of interest that in the aforementioned paper on weight reduction by Patel and Stowers the addition of the potent insulin stimulator, sulfonylurea, to phenformin treated patients resulted in a weight loss less than in patients receiving phenformin alone. In another study West and Tophoj, using a different sulfonylurea, chlorpropamide, in a dose of 125 to 250 mg given for three to twenty-six months, showed a weight gain in eighteen of twenty-three patients though the control of diabetes was unsatisfactory in many of the subjects (19).

How exactly does phenformin accomplish the opposite of insulin or the oral sulfonylureas? The mechanism of action of phenformin on carbohydrate metabolism is disputed. Originally it was shown that phenformin in animals was followed by an increase in blood lactic acid and decreased oxygen uptake by the muscles. This, along with *in vitro* observations, suggested that phenformin acts simply by inhibiting aerobic (HMS) tissue metabolism. Two observations refute this premise. First, the concentrations employed in experiments varied between 10  $\mu\text{g/ml}$  and 1.7  $\text{mg/ml}$ . The maximum human therapeutic dose is 300 to 350 mg of phenformin daily, with a resulting tissue concentration below 5  $\mu\text{g/ml}$ . No cumulative effect is known. Secondly, other drugs such as barbiturates and phenothiazine tranquilizers may produce tissue hypoxia without a hypoglycemic effect (20-24).

A more reasonable explanation would appear to be an insulin potentiating activity effect either in the periphery or in the liver. If glucose could be utilized with a smaller concentration of insulin, this might result in less  $\text{CoII.H}_2$  available for the HMS pathway.

Grodsky demonstrated a hyperinsulin response by immunochemical assay after oral glucose in subjects with maturity-onset diabetes, obese non-diabetic subjects, and non-obese non-diabetic subjects with a strong family history for diabetes (25).

This is very interesting because it may mean we have been looking at only one side of the coin. We have always supposed that obesity predisposed one to diabetes. This was supported by the work of Randle who demonstrated F.F.A. from adipose tissue inhibited glucose utilization (26). Now turning the coin over we see that increased insulin response in the prediabetic can very well lead to obesity and this may be a consequence of early diabetes. If one



were to grade diabetics this would be stage I whereas diabetes as we know it today would be a consequence of exhaustion of the beta cells and/or insulin inhibition by blocking antibodies.

This response could be reduced consistently by phenformin. Butterfield also showed diminished insulin requirement by demonstrating that phenformin, as well as insulin or the sulfonylureas, could reduce the higher critical level of arterial blood sugar which must be exceeded before glucose can enter the cell in diabetic subjects (27).

The effect of phenformin on adipose tissue when employed in therapeutic concentrations has been shown by other investigators to significantly potentiate the action of insulin with an increase in glucose oxidation (28, 29).

Facts inconsistent with the insulin potentiating effect are that phenformin has no effect on the normal individual (30), and that the intravenous insulin tolerance test does not change in the presence of phenformin (31). The fact that phenformin is effective only in diabetic subjects does, however, suggest that perhaps phenformin interferes with the plasma insulin inhibitors. If it could be shown that the insulin bound fraction has an effect on hepatic or adipose tissue lipid synthesis while not exerting an effect on glucose, many paradoxes would be solved. Shoemaker, *et al.* have suggested this may be the case (32). The effect of phenformin would therefore be to inhibit insulin binding and its consequent effect on lipid synthesis. Clinically, therefore, one should find a fall in cholesterol and triglycerides as a primary effect and a glucose lowering effect if enough free or unbound insulin were available. In fact, with less circulating NEFA, glucose utilization could be efficient and the lowered blood glucose would provide a lessened stimulus for insulin production from the pancreas. With a decrease in bound insulin or even in total insulin, less HMS activity would be observed and weight loss could result, as demonstrated in this paper. We in fact studied these patients to see if the phenformin treated subjects had a lower cholesterol and triglyceride level. This indeed was the case, supporting the above hypothesis. This will be reported in a subsequent paper.

#### CONCLUSION

Phenformin in combination with insulin or tolbutamide improved the control of 63% of subjects previously poorly controlled, regardless of age, sex, duration of diabetes, population group, family history or blood pressure.

A significant weight loss of more than 5 pounds occurred in 36% of all subjects. Patients receiving 100 to 150 mg of phenformin had twice as much chance of losing significant weight as patients receiving 50 mg. Higher dosage also correlated with greater weight reduction, i.e., 11 out of 22 patients losing more than 5 pounds lost more than 10 pounds when taking 100 to 150 mg whereas only 1 out of 4 other patients taking 50 mg lost a comparable amount of weight. There was also greater loss of weight with longer duration of treatment.

It is suggested that insulin in bound form or in excess provides a stimulus for shunt activity with body storage and weight gain. Phenformin, by lowering

total insulin requirement or inhibiting insulin binding, makes less insulin available for the shunt, and therefore, produces less tendency for weight gain. Phenformin is recommended as an important adjunct to the treatment of the obese diabetic. Since cholesterol and triglycerides are also lowered by employing the E-M metabolic pathway, phenformin could be recommended as a possible tool to lessen the rapidly progressive atherosclerosis of the diabetic individual. A subsequent paper is concerned with this problem.

## REFERENCES

1. Hoffman, S. S.: A Rapid Photoelectric Method for the Determination of Glucose in Blood and Urine. *J. Biol. Chem.*, 120: 51, 1937.
2. Beaser, S. B.: Oral Treatment of Diabetes Mellitus. *J.A.M.A.*, 187: 887, 1964.
3. Krall, L. P., and Bradley, F. F.: Long Term Phenformin Therapy for Diabetics. *Geriatrics*, 17: 337, 1962.
4. Dolger, H.: Personal communication.
5. Barclay, P. L.: Clinical Evaluations of Phenformin in Office Practice. *J.A.M.A.*, 174: 474, 1960.
6. Patel, D. P., and Stowers, J. M.: Phenformin in Weight Reduction of Obese Diabetics. *Lancet*, 2: 282, 1964.
7. Moss, J. M., DeLawter, D. E., Tyröler, S. A., and Field, J. B.: Phenformin in Diabetic Treatment. *Medical Times*, 89: 561, 1961.
8. Weller, C., Donesa, A., and Linder, M.: The Phenformin Timed-Disintegration Capsule (DBI-TD) in the Management of Previously Treated Diabetic Patients. *Metabolism*, 11: 1134, 1962.
9. Radding, R. S., McHenry, J. I., Pudie, C. B., and Robins, O.: The Use of Acetohexamide in Stable Diabetes Mellitus. *Metabolism*, 12: 311, 1963.
10. Dickens, F.: Disorders of Carbohydrate Metabolism. Proceedings of a Conference held by the Royal College of Physicians of London, 1962.
11. Siperstein, M. D.: Inter-relationships of Glucose and Lipid Metabolism. *Am. J. Med.*, 26: 658, 1959.
12. Hollifield, G., and Parson, W. J.: Metabolic Adaptions to a "Stuff and Starve" Feeding Program. *J. Clin. Invest.*, 41: 245, 1962.
13. Gordon, E. S., Goldberg, M., and Chosey, G. J.: A New Concept in the Treatment of Obesity. *J.A.M.A.*, 186: 50, 1963.
14. Fabry, P., Fodor, J., Hejl, Z., Braun, J., and Zvolankova, K.: The Frequency of Meals: Its Relation to Overweight Hypercholesterolemia and Decreased Glucose Tolerance. *Lancet*, 2: 614, 1964.
15. Keys, A., Anderson, J. T., and Grande, F. J.: Diet-Type (Fats Constant) and Blood Lipids in Man. *J. Nutr.*, 70: 257, 1960.
16. Winegrad, A. I., and Renold, A. E.: Studies on Rat Adipose Tissue in Vitro. I. *J. Biol. Chem.*, 233: 267, 1958.
17. Glock, G. E., and McLean, P.: Pathways of Glucose Utilization in Mammary Tissue. *Proc. R. Soc. Ser. B., Biol. Sc.*, 149: 351, 1958.
18. Field, J. B.: Clinical and Biological Studies in Patients with Functioning Islet Cell Tumors. *Am. J. Med.*, 36: 867, 1964.
19. West, K. M., and Tophøj, E.: Effect of Unrestricted Diet on Diabetes During Therapy with Chlorpropamide. *Metabolism*, 10: 689, 1961.
20. Williams, R. H., Tanner, D. C., and Odell, W. D.: Hypoglycemic Actions of Phenethyl-anyl and Isoamyl Diquanide. *Diabetes*, 7: 87, 1958.
21. Steiner, D. F., and Williams, R. H.: Actions of Phenethylbiquanide, a Hypoglycemic Agent on Tricarboxylic Acid Cycle, *Metabolism*, 9: 36, 1960.
22. Steiner, D. F., and Williams, R. H.: Respiratory Inhibition and Hypoglycemia by

- Biquanides and Decamethylene Diquanides. *Biochem. et Biophys. Acta.*, 30: 329, 1958.
23. Unger, G., Psychoyos, S., and Hall, H. A.: Action of Phenethylbiquanide, a Hypoglycemic Agent of Tricarboxylic Acid Cycle. *Metabolism*, 9: 36, 1960.
  24. Clarke, D. W., and Forbath, N.: The Effect of Phenethylbiquanide Upon the Metabolism of the Isolated Rat Diaphragm. *Metabolism*, 8: 195, 1959.
  25. Grodsky, G. M., Karam, J. H., Fotios, C. P., and Forsham, P. H.: Reduction by Phenformin of Excessive Insulin Levels After Glucose Loading in Obese and Diabetic Subjects. *Metabolism*, 12: 178, 1963.
  26. Hales, C. N. and Randle, P. J.: Effects of Low-carbohydrate Diet and Diabetes Mellitus on Plasma Concentrations of Glucose, Non-esterified Fatty Acid, and Insulin During Oral-Glucose Tolerance Tests. *Lancet*, I: 790, 1963.
  27. Butterfield, J., Fry, I. K., and Halling, E.: Effects of Insulin, Tolbutamide, and Phenethylbiquanide on Peripheral Glucose Uptake in Man. *Diabetes*, 7: 449, 1958.
  28. Darveke, H., and Bach, I.: Experimental Studies on the Mode of Action of Biquanides. *Metabolism*, 12: 319, 1963.
  29. Correa, P. R.: Influence of DBI Concentration in Medium Upon Isolated Fat Tissue Activity. *Metabolism*, 13: 496, 1964.
  30. Unger, G., Freedman, L. and Shapiro, S. L.: Pharmacological Studies of a New Oral Hypoglycemic Drug. *Proc. Exper. Biol. Med.*, 95: 190, 1957.
  31. Fajans, S. S., Moorhouse, J. A., Doorenbos, H., Louis, L. H., and Conn, J. W.: Metabolic Effects of Phenethylbiquanide in Normal Subjects and in Diabetic Patients. *Diabetes*, 9: 194, 1960.
  32. Shoemaker, W. C., Ashmore, J., Carrothers, P. J., and Schulman, M.: Effect of Insulin on Rate of Hepatic Uptake of NEFA. *Proc. Soc. Exp. Biol. Med.*, 103: 585, 1960.

TABLE I  
*Composition of Clinic and Study Group*

	Numbers	Male	Female	% White	% Puerto Rican	% Negro
Total Population	627	164	463	46	30	24
Population Employed in Study	72	14	58	38	24	38

TABLE II  
*Glucosuria Improvement with DBI*

	Total No. Subjects	Improved	Same	% Improvement
Mode of Therapy				
DBI and Insulin	18	8	10	44
DBI and Orinase	42	30	12	71
Any DBI Combination	60	38	22	63
Sex				
Males				
DBI and Insulin	5	0	5	—
DBI and Orinase	8	7	1	88
Any DBI Combination	13	7	6	54
Females				
DBI and Insulin	13	8	5	61
DBI and Orinase	34	23	11	68
Any DBI Combination	47	31	16	66

TABLE III  
*Factors Related to Efficacy of DBI Therapy*

	Number of Subjects	* Im- proved Sub- jects	% Improved	No. "Same" Subjects	% "Same" Subjects
Population Group					
White	23	16	70	7	30
Puerto Rican	24	15	62	9	38
Negro	13	7	54	4	46
Age					
20-34	4	1	25	3	75
35-59	26	17	68	8	32
60-80	32	20	65	11	35
Duration of Diabetes					
Less than 5 yrs.	23	16	69	7	31
5-10 yrs.	23	11	48	12	52
10+ yrs.	14	11	78	3	22
Family History of Diabetes					
Positive	21	14	67	7	33
Negative	34	23	68	11	32
Diastolic Blood Pressure					
>90 mm Hg	11	9	82	2	18
<90 mm Hg	40	28	70	12	30

TABLE IV  
*DBI and Weight*

	Number	Lost > 5	Gained > 5	No Change in Weight	% Losing	% Gaining	% No Change
Relationship of Change in Weight to Type of Drug Therapy							
DBI and Insulin	19	7	6	6	37	31.5	31.5
DBI	8	3	4	1	37.5	50.0	12.5
DBI and Orinase	45	16	4	25	35	9	56.0
	72	26	14	32	36% of total	19% of total	45 of total
Control on DBI, with Insulin or Orinase							
Patient Improved	38	11	7	20	29	18	53
Patient Unimproved	22	8	2	12	36	9	55
	60	19	9	32	32	15	53
Dosage of DBI							
50 mg	19	4	5	10	21	26	53
100 mg	28	11	3	14	40	10	50
150 mg	25	10	6	8	40	25	33
Degree of Control in Patients on 150 mg							
Control Improved	9	3	3	3	33.3	33.3	33.3
Control Unimproved	11	5	1	5	45.5	9	45.5

*Dosage of DBI and Weight Loss*

	Weight Loss	# of Subjects	% Losing 10 lbs. +
Dosage			
50 mg	5-10	3	
	11-15	1	25
	16-20		
	21+		
100 mg	5-10	5	
	11-15	1	55
	16-20	3	
	21+	2	
150 mg	5-10	6	
	11-15	3	46
	16-20	1	
	21+	1	

*Weight Loss Based on Duration of Treatment*

Weight loss based on duration			
6-12 months	5-10	7	30
	11-15	2	
	16-20	1	
	21-25		
13-25 months	5-10	7	56
	11-15	3	
	16-20	3	
	21-25	2	
	26+	1	



TABLE V  
*Factors Influencing Change in Weight*

	Gained > 5	Lost > 5	Same
Sex			
Males	3	4	
Females	12	22	
Age			
20-34	1	1	
35-59	7	7	
60-80	7	18	
Duration of Diabetes			
5	1	12	
5-10	6	7	
10	8	7	
Population Group			
White	10	10	
Puerto Rican	4	7	
Negro	4	9	
Body Weight			
Underweight	0	1 (25%)	3
N1-25% over	4	7 (47%)	4
26-50% over	2	9 (47%)	8
50-100% over	2	5 (33%)	8
100% & over	2	2 (20%)	6
Weight Loss > 5 lbs.	26 patients		
Range 5-33			
Median 11			

## CLINICO-PATHOLOGICAL CONFERENCE

### Abdominal Pain, Skin Lesions, and Shock in an Elderly Woman

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A 92 year old white female was admitted to The Mount Sinai Hospital because of abdominal pain, diarrhea and shock.

A diagnosis of chronic lymphatic leukemia with hepatosplenomegaly was established approximately five years prior to admission and the patient received radiotherapy for an enlarged spleen. She was also found to be in congestive heart failure with bilateral pleural effusions and ascites which responded well to digitalis and diuretics and she was maintained on digitalis and chlorothiazide in addition to prednisone (5 mg per day) until one year prior to admission. Ten days prior to admission she developed epigastric pain. Donnatal and milk of magnesia decreased the intensity of the pain; however, five days prior to admission her family noted her urine to be bloody. She was seen by her private physician who also noted a mild temperature elevation and placed her on tetracycline therapy. Two days later she developed a severe non-bloody diarrhea, unresponsive to tincture of opium and sulfasuxidine. Two days prior to admission she was noted to be groggy and unresponsive. Oral intake during this period was poor. On the day of admission her private physician found her to be unconscious with a blood pressure of 70/40, and a distended, tender abdomen.

At age 76 she had an appendectomy for acute appendicitis and at age 82 a repair of an incarcerated femoral hernia. The recorded blood pressures on these admissions were 180/86 and 190/100, respectively.

She was an elderly white female who only responded to loud noises by blinking. Her eyes were deviated to the right and the pupils did not react to light. The blood pressure and radial pulse were unobtainable, but a pulse could be palpated in the right femoral artery. The respirations were 36 per minute and the temperature was 101°. Vesicles containing yellow fluid with hemorrhagic bases were scattered over the neck, chest, abdomen and inguinal regions. Petechial and purpuric hemorrhages were also noted over the neck, chest and extremities. The PMI was not palpable. The heart beat was irregular and a grade II precordial systolic murmur was heard. Rales were heard at the left lung base. The abdomen was distended, tympanitic, with rebound tenderness most marked on the right side. Bowel sounds were absent. The liver was not palpable but the tip of the spleen was felt. Firm lymph nodes up to 1 cm in size were palpated in both axillae. The extremities were cold and spontaneous movements of the right lower extremity were noted.

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The hematocrit was 53% and the white blood count was 20,000 per mm<sup>3</sup> with 57% lymphocytes. The urine contained red and white cell casts. The stool was semifirmed, brown and had a 2 plus guaiac reaction. Abdominal x-ray revealed an ileus pattern with dilated loops of small intestine. The chest x-ray revealed the heart to be slightly enlarged. The ECG showed atrial fibrillation with a ventricular rate of 66 per minute, left axis deviation, left ventricular hypertrophy and ST depression in the lateral precordial leads. The spinal fluid was clear and contained 9 crenated red blood cells per mm<sup>3</sup>. The cerebrospinal fluid pressure was not obtained.

The patient was placed on high doses of penicillin, chloramphenicol and corticosteroids. Intravenous fluids and vasopressors were administered. An abdominal paracentesis was performed and yielded 2 ml of yellow fluid containing red blood cells. A surgical consultant saw the patient and felt the patient's clinical condition precluded operative intervention. The patient died 18 hours after admission to the hospital.

*Dr. Mortimer E. Bader:*\* This is an interesting case of a 92 year old white female who entered the hospital with abdominal pain, diarrhea and shock. The patient had chronic lymphatic leukemia with hepatosplenomegaly of approximately five years duration, at which time she received radiotherapy to her enlarged spleen. Her spleen tip was palpable at the time of examination and therefore was unlikely a cause for an acute abdominal catastrophe. Five years ago she also had congestive heart failure with bilateral pleural effusions and ascites. She had an abnormal electrocardiogram showing atrial fibrillation. In a woman 92 years old, with a history of hypertension, it would be reasonable to make a diagnosis of arteriosclerotic and hypertensive heart disease with heart failure, which incidentally responded very well to digitalis and hydrochlorothiazide. There is no comment made as to whether she received plain hydrochlorothiazide or hydrochlorothiazide with potassium since the use of both potassium and chlorothiazides can produce small bowel ulceration and secondary obstruction. This might have accounted for the epigastric pain, but I think we can dismiss it. She had been on corticosteroids which may also produce ulcerations but that is unlikely since corticosteroids were discontinued a year prior to admission. A patient with chronic lymphatic leukemia with diminished resistance to a variety of pathogens would certainly make me think of sepsis, particularly gram negative sepsis with irreversible shock and death. As a consequence of their lowered resistance, patients with lymphatic leukemia have a higher incidence of Salmonella infections which could also explain the episode of diarrhea and may have been a possible source of a gram negative sepsis.

On admission, she only responded to loud noises. Her response to such stimuli was to blink. Her eyes were deviated to the right and the pupils did not react to light. Deviation of the eyes to the right would suggest that she either had a left mid-brain lesion, or a right cerebral lesion. It is unclear whether the spontaneous motion in her right lower extremity represented a

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clonic type of seizure or was voluntary motion. If it were a clonic seizure, it would not be compatible with a lesion in the left mid-brain alone, since Dr. Nathanson of this hospital has shown that left mid-brain lesions produce ipsilateral involvement, not contralateral involvement. I have difficulty explaining her central nervous system findings, except to say that they suggest a focal lesion and possibly more than one. In a woman 92 years old, with probably cerebral vascular disease, a drop in perfusion pressure would be sufficient to produce a syndrome of vascular insufficiency. Certainly, tilt table experiments which drop pressure just forty or fifty millimeters of mercury will produce full-blown focal cerebral patterns in people with pre-existing vascular disease. Did she have an encephalitis? This is not likely because the spinal fluid contained only red cells. Large numbers of white cells are usually found in encephalitis and leukemic involvement of the central nervous system would hardly account for the acuity of this syndrome.

Petechial and purpuric hemorrhages were also noted over the neck, chest and extremities. In a patient in shock, the latter would certainly suggest the Waterhouse-Friedrickson syndrome.

She had a hematocrit of 53%, which I suspect represented some hemoconcentration, and the white blood count was 20,000 with 57% lymphocytes. The urine contained red and white cell casts. The stool was semiformal, brown, and had a two-plus guaiac reaction. This is important. If we are considering an acute abdominal catastrophe on a vascular basis, we would expect to find some blood in the gut. In a patient with known atrial fibrillation, it is possible that she had a mesenteric thrombosis or embolism to the mesentery and/or kidney. This would account for her shock and her acute abdominal pain, ileus, and the terminal episode. However, I would expect perhaps a little more blood in the gut.

I think we can make a diagnosis of arteriosclerotic and hypertensive heart disease with treated congestive failure. However, this is not the primary diagnosis in this case. She was treated with antibiotics, vasopressors and intravenous fluids. I suspect a clinical diagnosis of sepsis had been made, which is most reasonable in light of the course and the preceding diagnosis. Abdominal paracentesis was performed and yielded two milliliters of yellow fluid containing some red blood cells. If we consider that she had sepsis, we could say that she had renal infection, gram negative in type, possibly associated with *Salmonella* in the gut. She had the shock that goes with it, the purpuric hemorrhagic lesions which are sometimes seen in shock-like states and a source in the urinary tract. Notwithstanding any of this, I believe she had some infection but it is not the reason this case was presented.

Periarteritis nodosa could explain the hemorrhagic Schwartzman-type lesions of the skin, but I have never seen or read of vesicular eruptions with necrotizing arteritis involving the mesentery and the skin. The finding which I think is the most critical in this case, and the only one which gives some clue, is the vesicular lesions containing yellow fluid on hemorrhagic bases scattered over the neck, chest, abdomen and inguinal regions. In my opinion,

those lesions represented generalized Herpes zoster. Generalized Herpes zoster very rarely occurs in people who do not have pre-existing lymphoma, Hodgkin's disease or lymphatic leukemia. Indeed, I think, in general, of all cases of generalized Herpes zoster almost 95% or more occur in persons with pre-existing lymphatic leukemia or Hodgkin's disease, unless one considers chickenpox as a common form of it. In lymphatic leukemia I do not know its precise incidence, but figures as high as 8% have been reported in Hodgkin's disease. The disease may appear anywhere from one and a half to eleven years after the onset of a lymphoma, but it is interesting that the generalized form usually appears about four or five years after the onset of the lymphoma. The presence of actual tumor tissue near the nerve root has been considered an important predisposing factor, particularly in localized Herpes zoster. There is a question whether radiation, alkylating agents and corticosteroids are also predisposing factors. This patient received no such major therapy and her steroids had been stopped a year before. In general, no conclusive statement can be made that corticosteroid therapy or the use of alkylating agents seem to make the incidence higher, particularly since they are used in the more severe cases in which Herpes zoster might be anticipated anyway. Herpes zoster commonly is associated with chickenpox or varicella infections. In fact, in the 1880's, Bokay of Budapest showed in several instances that chickenpox epidemics followed outbreaks of Herpes zoster. It is now well established that there is a relationship between the two, although there are some interesting exceptions to the rule. For example, in Tristan da Cunha, an island not noted for its infectious diseases, there were several cases of Herpes zoster without any chickenpox appearing in a population group who apparently had no immunity to chickenpox. In the Shetland Islands, they had varicella after an attack of Herpes zoster when there was apparently no previous source for varicella on the islands. In 1954, a woman was admitted to this hospital who had generalized Herpes zoster and the lesions were similar to those in the present case. The pictures are available in *The Journal of The Mount Sinai Hospital*, in an article by Dr. Howard L. Moscovitz. Fourteen exposed adults subsequently contracted chickenpox.<sup>1</sup> Immunologic studies are of some interest. Twenty-eight children were inoculated with the fluid from vesicles of Herpes zoster and three of them developed typical varicella and seventeen developed some form of papular vesicles. A similar reaction could not be induced in children who were already immune to varicella. In both groups, complement fixation reactions were elicited using either varicella crusts or Herpes zoster fluid and convalescent serum. I believe then that this 92 year old lady with chronic lymphatic leukemia had Herpes zoster. I also believe that the epigastric pain she had was somehow related to this and she died of overwhelming toxicity. I have looked in vain for some evidence of visceral involvement and I am not familiar with any. Perhaps I can learn

<sup>1</sup>Moscovitz, H. L. Generalized Herpes Zoster Initiating a Minor Epidemic of Chickenpox. *J. Mt. Sinai Hosp.* 22: 79, 1955.



something about it today. The usual cause of death in these people is pneumonia or encephalitis.

My final diagnoses are: 1) chronic lymphatic leukemia; 2) arteriosclerotic and hypertensive heart disease with an enlarged heart; and 3) generalized Herpes zoster. The toxicity from the latter led to her demise.

*Question:* How do you explain the renal lesions?

*Dr. Bader:* The urinary sediment was consistent with a hemorrhagic urinary tract infection.

*Question:* Do you think the picture might be consistent with gram negative sepsis?

*Dr. Bader:* I think gram negative sepsis would have been a perfectly reasonable explanation and ordinarily I would say that a patient with lymphatic leukemia who presents with shock after a urinary tract infection has a gram negative sepsis.

*Question:* Do patients with purpura develop intestinal lesions?

*Dr. Bader:* I heard there was a case in the hospital not too long ago where necrotizing lesions were found; indeed, Dr. Parets had a case of a Herpes zoster who had transient jaundice and necrotizing lesions of the liver and the mesentery, so it is perfectly possible that she had some necrotizing lesion of the bowel as a consequence of this herpetic infection.

*Dr. I. William Grossman\*:* At autopsy, this patient showed the usual findings of chronic lymphatic leukemia. The vertebral marrow and femoral marrows were red with focal pale gray areas. Microscopic examination revealed a hypercellular marrow infiltrated by lymphocytes (Fig. 1). The visceral and superficial lymph nodes were enlarged and the normal architecture was obliterated by lymphocytic infiltration. The patient also had chronic cholecystitis with cholelithiasis. And, as Dr. Bader mentioned, the patient had a large heart with left ventricular hypertrophy and marked coronary arteriosclerosis and the left kidney was contracted as a result of old vascular disease. The etiology of this woman's hematuria was a very fulminant, hemorrhagic cystitis. Gross examination of the stomach and esophagus revealed diffuse discrete erosions and ulcerations (Fig. 2). Microscopic examination of the squamous mucosa of the esophagus adjacent to the erosions contained intranuclear inclusions. The stomach showed areas of hemorrhagic necrosis of the epithelium with intranuclear inclusions in the remaining glandular elements. Intranuclear inclusions were also seen throughout in the small and large intestinal epithelium. There were areas of hemorrhage on the capsular surface of the liver and, on the cut surface, numerous focal areas of necrosis were seen. Microscopically, these necrotic areas resembled infarcts with a scant inflammatory infiltrate (Fig. 3). Intranuclear inclusions were seen in occasional hepatocytes and in the bile duct epithelium. The portal tracts contained lymphocytic infiltrates as seen in chronic lymphatic leukemia. The spleen was enlarged and weighed 385 grams.

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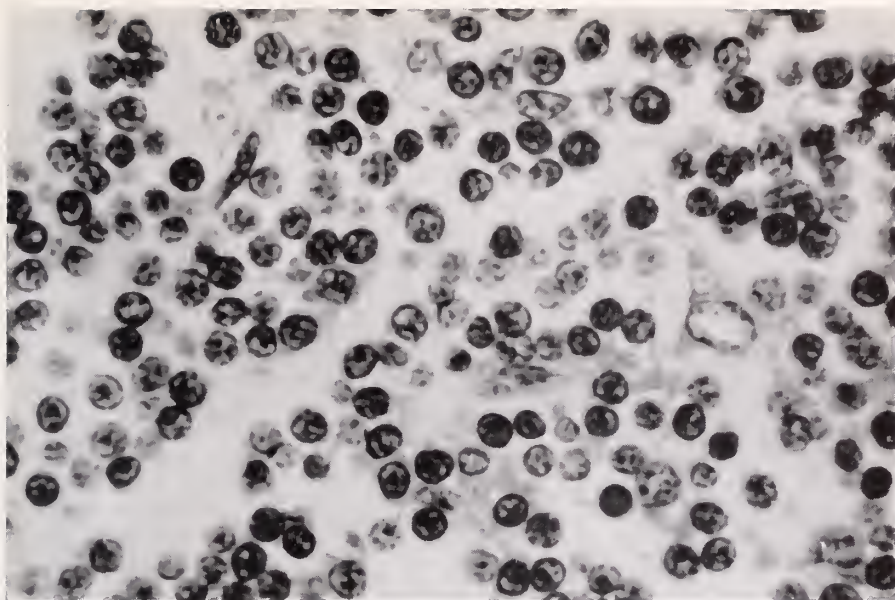


FIG. 1. Bone marrow showing a lymphocytic infiltration (H & E  $\times 400$ ).



FIG. 2. Focal hemorrhagic necrosis of the epithelium of the stomach (H & E  $\times 40$ ).

The cut surface displayed nodular infiltrates which on microscopic examination were found to be collections of lymphocytes extending from the follicles. Areas of necrosis were found within the lymphoid collections and intranuclear inclusions could be seen within cells in the necrotic areas.

The pancreas displayed multiple focal areas of hemorrhage and ischemic necrosis and microscopic examination revealed no residual pancreatic tissue in some areas. Intranuclear inclusions were seen within intact pancreatic acinar cells (Fig. 4). There was an interstitial pneumonitis and within the alveolar lining cells, intranuclear inclusions were also found.

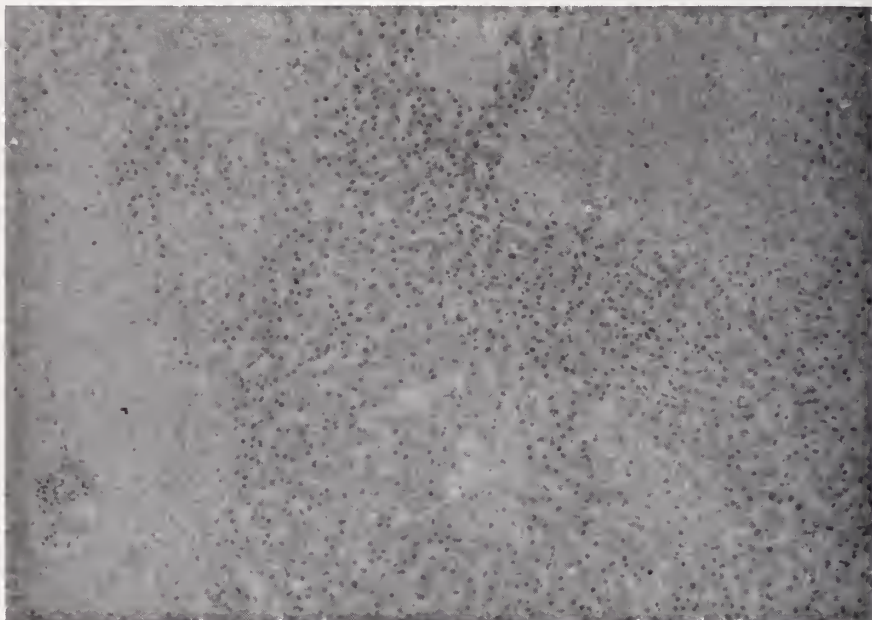


FIG. 3. Focal necrotic areas within the liver resembling infarcts with a scant inflammatory infiltrate (H & E  $\times 40$ ).

The skin of this patient, as was described in the protocol, showed vesicles with hemorrhagic bases.

Low power microscopic examination revealed these vesicular lesions to be intraepidermal and unilocular. Giant cells with intranuclear inclusions were seen on higher-power examination (Fig. 5). It is interesting to note several of the skin lesions were at an earlier stage of development and intercellular edema was seen to surround the infected cells. Subsequently, the infected cells lose their attachment to their neighboring cells and form large intraepidermal vesicles. The dermis of the skin showed focal small vessel wall necrosis which accounted for the hemorrhage at the base of the vesicles. Intranuclear inclusions were also found in the endothelial cells of the dermal capillaries. With the Feulgen reaction which stains DNA red, a halo was seen



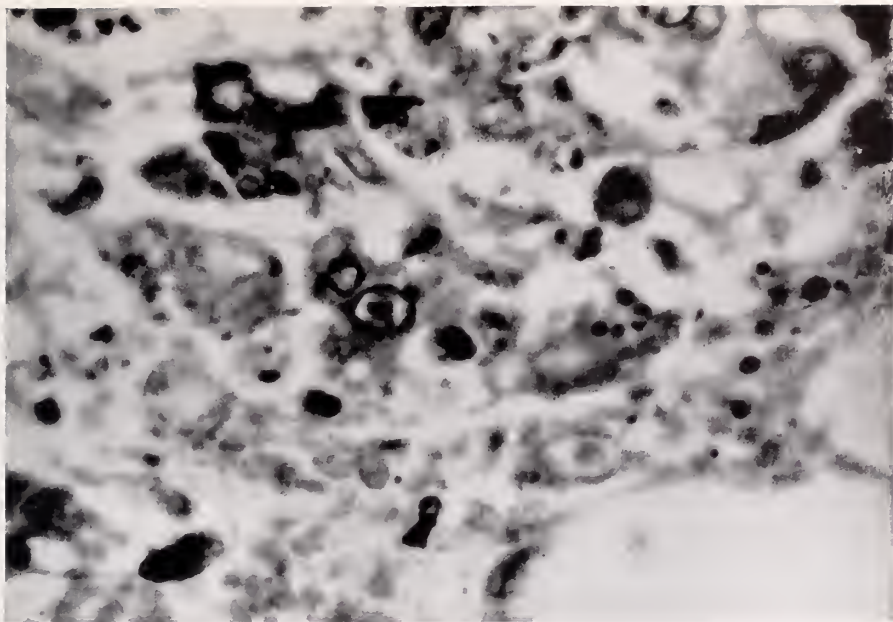


FIG. 4. Intranuclear inclusions within pancreatic acinar cells (H & E  $\times$  400).

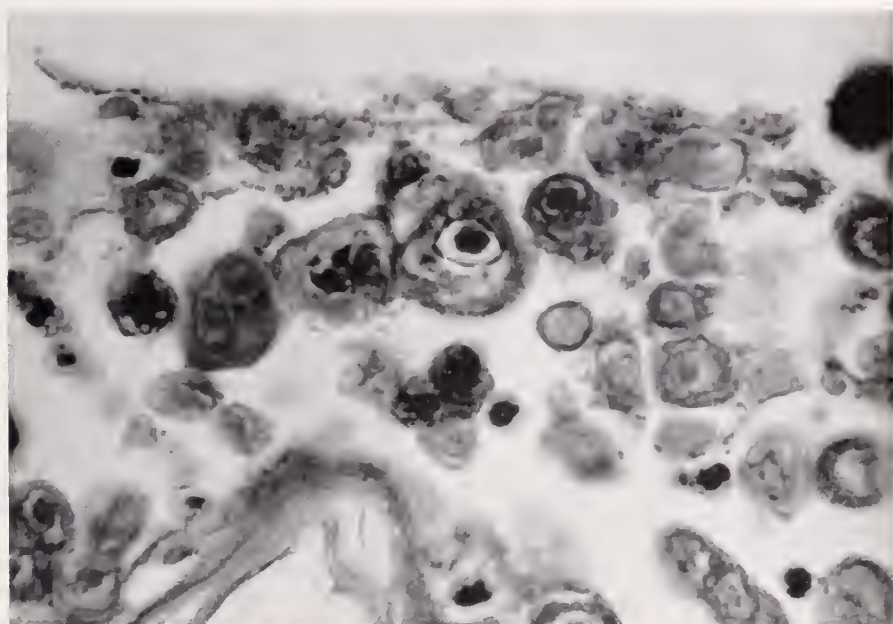


FIG. 5. Intranuclear inclusions within cells of the epidermis (H & E  $\times$  400).

around the intranuclear inclusions. Since older lesions lose the Feulgen staining reactions, it is positive in only occasional intranuclear inclusions of the skin. This suggests that the virus particles are most probably denatured. The lesions in the skin and in the viscera in this patient could have been caused by one of two viruses; varicella-zoster or Herpes simplex.

Intranuclear inclusions were found in ganglion cells of the pancreas and gastrointestinal tract in this patient which, only occur in varicella-zoster infection.

In summary, I agree entirely with Dr. Bader's diagnosis. This patient did have chronic lymphatic leukemia and she developed generalized varicella-zoster virus infection with diffuse visceral involvement although the patient had no history of contact with the varicella-zoster virus. The diffuse gastrointestinal erosions and ulcerations and the extensive hemorrhagic necrosis of the pancreas most likely accounted for the patient's epigastric pain and diarrhea.

I feel the overwhelming viral infection led to the death of this patient, as Dr. Bader correctly surmised.

Are there any other questions or comments?

*Question:* What was the cause of the hemorrhagic cystitis?

*Dr. Grossman:* I did not see any intranuclear inclusions in the bladder, so I am at a loss to explain its etiology.

*Dr. Wasserman:* In our series here, I would venture to say that about 50% of our patients with lymphoma have signs of Herpes zoster some time during their course.

*NOTE:* This case is being prepared for publication by Dr. W. Grossman.



## FOREWORD

This monograph, *The Approach to Diagnosis in Modern Neurology*, is a joint effort by the Neurological Staff of The Mount Sinai Hospital (a few contributors are former members). The guest editor is Dr. Morris B. Bender, the dynamic Director of the Department of Neurology, and his large staff of outstanding neurologists. As the title indicates, emphasis is on the "approach" to diagnosis and the focus is on the patient at the bedside. Sophisticated modern techniques not available two decades ago are presented, not as isolated disciplines or free-standing entities, but from the viewpoint of their usefulness and limitations in diagnosis. It is hoped that Residents in Neurology, internists who meet neurological problems, and the interested general practitioner will find pleasure and profit in it; this is the level at which it is written. Perhaps the mature neurologist may find something of interest also.

This monograph could not have been assembled without the intelligent, tireless efforts of Dr. Martin Feldman as Assistant Editor. As always we are in debt for the technical help of Mrs. Joann Slatt, Executive Assistant to the Journal.

Lester R. Tuchman, M.D.

Editor

Journal of The Mount Sinai Hospital

## Introduction

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The Department of Neurology at The Mount Sinai Hospital is one of the oldest in the United States and has always emphasized the clinical aspects of disease of the nervous system. Before 1935 the neurologist depended on careful history and meticulous examination in his attempts to localize and find the cause of the lesion. In those days there were few laboratory tests which were of aid in the diagnosis. Electroencephalography, pantopaque myelography, and carotid arteriography were introduced after 1935 and even then one depended on the neurosurgeon's ventriculogram or exploratory operation for a more precise diagnosis. It was only during the past two decades that clinical neurology became enriched with new diagnostic techniques and modification of the old. With this the standard neurologic examination at this hospital has been simplified and modified. Some of the innovations and modifications in the bedside examinations are to be described in the ensuing articles.

In general, it is still the history and clinical examinations which aid us in the anatomic localization. The determination of the etiology, however, is much more difficult. In most cases it can be ascertained only by special or routine laboratory studies. The routine studies consist of urinalysis, blood count, sedimentation rate, chemistry, serology, X-rays of the skull and chest, and the diagnostic lumbar puncture. The special laboratory tests consist of clinical neurophysiology and neuroradiologic studies. In some instances special neurochemical analyses of the spinal fluid are useful. Recently increasing number of muscle biopsies have been used in our classification of neuromuscular disorders.

Of all the special tests, neuroradiology is the most useful. It has revolutionized the diagnosis and treatment of diseases of the nervous system. Cerebral neoplasms, subdural hematomas and occlusive disease of vessels in the neck or brain may be uncovered in unsuspected cases. The treatment of these entities has also been changed. Whereas in previous years all suspected intracranial masses were "attacked" surgically there is now a greater reluctance to "explore" or excise neoplasms. Deeply situated or otherwise inaccessible tumors which are highly vascular, such as glioblastoma, or multiple tumors, as in metastatic disease are treated with radiotherapy. These masses can now be recognized by cerebral angiography and do not require diagnostic or therapeutic cranial surgery (1). Moreover, subdural hematomas are no longer diagnosed through burr holes and treated routinely by evacuation. The carotid arteriogram (frontal view) establishes the diagnosis. If the patient does not appear too ill he is treated symptomatically and his course monitored by serial angiography or brain scanning. Many such patients improve spontaneously (2). During the past six years there were twenty-four patients with subdural hematoma at The Mount Sinai Hospital and nine in other institutions who recovered without surgery.

With the aid of cerebral angiography the diagnosis and treatment of subarachnoid hemorrhage has also been modified. Intracranial leaking aneurysm may be located accurately so that appropriate treatment may be instituted. Some cases of so-called "epilepsy," bizarre seizure disorders or migraine have been reclassified as arteriovenous anomalies. Intracerebral hematomas, or cerebral edema due to infarction may also be detected by angiography. Besides angiography there are other neuroradiologic methods which are used in the discovery of the location and nature of the disease process. Pneumoencephalography, using various fractionation techniques, may reveal tumors or enlargement of one or more ventricles due to a variety of causes. Details of pathology in the posterior fossa can be uncovered by contrast studies through the endolumbar route. This method is superior to surgical ventriculography because it outlines extraventricular spaces and there is no damage to brain tissue as may occur during the introduction of the needle into the lateral ventricle. Lesion distorting the fourth ventricle or the cisterns in the posterior fossa can be demonstrated by pneumoencephalography or by pantopaque introduced through a lumbar puncture. The latter is a simple technique which is not painful and does not produce severe after-effects. With pantopaque myelography one may distinguish between extra and intradural tumors or intramedullary neoplasms of the spinal cord. This may also demonstrate arteriovenous anomalies of the spinal cord, spinal arachnoiditis, ridging causing compression of the cord and herniation of intervertebral discs. In the performance of diagnostic lumbar puncture, pneumoencephalography or myelogram intrathecal injection of 40 milligrams of Depo-Medrol is given at the end of the procedure. Such injection tends to minimize the headache and other reactions associated with these tests.

The neuroradiologic techniques and other well established as well as more recent diagnostic aids are part of new neurologic subspecialties, namely electroencephalography, electromyography, electro-oculography, and sonoencephalography. All of these are used in our department and some of the techniques will be reported.

In general, the clinical and laboratory examinations aid us in the establishment of location, nature of the pathologic condition, and in the type of treatment to be instituted. Besides the clinical value, the performance of these examinations often reveals data which are useful in our staff research projects and in the education of our trainees.

#### REFERENCES

1. Bender, M. B., and Elizan, T. B.: The Non-surgical Management of Brain Tumors. *Tr. Am. Neurol. A.*, 87: 20, 1962.
2. Bender, M. B.: Recovery from Subdural Hematoma without Surgery. *J. Mt. Sinai Hosp.*, 27: 52, 1960.

## PART I. CLINICAL BEDSIDE EXAMINATIONS

### Classification of Neurologic Disorders

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Some physicians have the mistaken impression that clinical diagnosis of the nervous system is exceptionally complex. Although it is true that the classical approaches to neurologic diagnosis emphasized and dwelt upon minute anatomic localization of lesions, we have used a less specific anatomic classification for many years with success. In fact we have used a simplified approach in our diagnostic thinking by classifying information first in terms of symptoms, second in terms of anatomy, and last in terms of etiology.

#### Symptomatic Classification

The *symptomatic* classification is not difficult. It is actually a translation of the patient's complaints into Latin, Greek or other language or the labeling of a group of symptoms with a name; eponymic syndromes. Thus the patient complaining of pain in the face is said to have a trigeminal neuralgia or tic douloureux. If the patient complains of dizziness, noises in the ear and deafness, he has Ménière's Disease. Paralysis of one half of the body is classified as hemiplegia and paralysis of both legs as paraplegia. Dyskinesia, tremor, hemianopia, diplopia, aphasia, dysarthria, coma, syncope, petit or grand mal are but a few other examples of acceptable symptomatic classification. Therefore every patient who has symptoms or a chief complaint can easily be classified. The problem is to relate the symptoms to a defect in nervous system structure and to find the cause of the defect. Often the problem is whether the symptoms are the result of one disease or complicated by coexistent conditions including psychogenic reaction.

#### Anatomic Localization

The *anatomic* localization is not difficult if one considers the symptoms and the findings in the examination of mental, motor and sensory functions as well as the reflexes and attempts to classify them according to the anatomic categories in the following Tables. The examiner will do well to decide first upon general regions such as brain as opposed to spinal cord. An excess concern over very minute localization is often unnecessary. Alterations in brain function may be recognized by the following symptoms and signs:

##### **Dysfunction of the Cerebrum:**

- (a) Convulsions or their equivalent
- (b) Mental and behavioral changes (organic type)

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- (c) Aphasia (disorder in language and communication)
- (d) Hemiplegia
- (e) Hemisensory defect
- (f) Homonymous field defects

**Dysfunction of the Basal Ganglia:**

- (a) Dyskinesias, such as tremors, choreas, athetoses, hemiballismus
- (b) Alterations in tone (hyper- and hypotonia)
- (c) Attitudinization
- (d) Alterations in posture and movement

**Dysfunction of the Cerebellum:**

Unsteadiness in motor performances (alterations in gait, adiadokokinesis, asynergia, ataxia, unchecked rebound, past-pointing)

**Dysfunction of the Brainstem (Midbrain, Pons and Medulla):**

- (a) Bilateral pupillary paralysis
- (b) Parályses of conjugate eye movements—horizontal, vertical or convergence
- (c) Crossed syndromes, such as paralysis of eyes, face or tongue; incoordination on one and sensory defect on opposite side of the body
- (d) Defects in articulation, vocalization, phonation, swallowing, and respiration
- (e) Nystagmus, particularly on upward gaze

The symptoms and signs of spinal cord dysfunctions are quite specific and are as follows:

**Dysfunction of the Spinal Cord:**

- (a) Bilateral involvement, particularly of the lower extremities
- (b) Presence of sensory levels
- (c) Impairment of motor function on one side and pain-temperature sensations on the other side
- (d) Impairment of vibration over the trunk and below
- (e) Urinary, rectal sphincter disturbances in absence of mental changes

Difficulty in anatomic diagnosis of lesions of the spinal cord arises when there is concomitant implication of the spinal root particularly when both are implicated and the symptoms of the latter mask those of the former.

**Dysfunction of the Spinal Roots:**

- (a) Sensory, motor and reflex changes in distribution of upper or lower spinal roots, unilateral (such as in cervical or lumbar herniated intervertebral disc syndrome) or bilateral (such as cauda equina root syndrome)
- (b) Involvement of all four extremities with impairment of sensory or motor deficits and depressed reflexes



Again there is difficulty in distinguishing between spinal root and peripheral nerve lesions. Lesions in spinal roots may produce symptoms and signs which resemble disease of peripheral nerves. Unless the history is definite such as in trauma, anatomic localization may be impossible as is sometimes the case in systemic disease such as diabetes or arthritis.

### **Dysfunctions of the Peripheral Nerves:**

- (a) Mononeuropathy—sensorimotor defects in the distribution of certain peripheral nerves
- (b) Polyneuropathy—sensorimotor defects with bilateral symmetrical glove and stocking distribution

### **Dysfunctions of the Cranial Nerves:**

Impairment of cranial nerve functions of peripheral origin especially the motor, are difficult to recognize for they may be confused with symptoms of lesions of the brainstem in which there may be impairment of ocular, facial, and bulbar functions. Alteration of the sensory cranial nerve functions namely defect in olfaction, vision, hearing, taste, and sense of balance are less difficult to identify.

## **Etiologic Classification**

The *etiologic* classification of neurologic disorder is most difficult. Besides history and examination one must rely on special laboratory tests. In order to search for a cause it is convenient to consider the following ten etiologic categories. Each of these is quite large and may be subdivided. The psychogenic group should be borne in mind in every classification. Psychogenic disorder can mimic neurologic conditions and appear superimposed on genuine neurologic syndromes.

- |                           |   |
|---------------------------|---|
| <b>1. Psychogenic</b>     | autonomic nervous system or somatic nervous system reactions, psychic.  |
| <b>2. Vascular</b>        | thrombosis, hemorrhage, embolism, spasm, insufficiency, aneurysm, blood dyscrasias and small blood vessel disease.                    |
| <b>3. Neoplastic</b>      | benign, primary, malignant, metastatic.   |
| <b>4. Toxic-Metabolic</b> | iatrogenic, drugs, metals, endocrine dysfunctions, protein, carbohydrate, lipid, electrolytes, nutritional, and vitamin deficiencies. |
| <b>5. Infections</b>      | viral, bacterial, parasitic, fungoid, and spirochetal.  |
| <b>6. Traumatic</b>       | concussion, contusion, laceration, fracture, herniations.   |

- |  |  |
|--|--|
| <b>7. Genetic and degenerative</b>               | demyelinating, sclerotic, atrophic, hypertrophic, abiotrophies, genetic disorders.                               |
| <b>8. Congenital and developmental anomalies</b> | cysts, tumors, defects, and malformations.   |
| <b>9. Osseous, arthritic and muscular</b>        | arthropathies with cervical ridging, compressions, and myopathies.   |
| <b>10. Idiopathic</b>                            | paroxysmal disorders without known cause such as Ménière's syndrome, migraine, epilepsies, neuralgias, and ties. |

After determining which part of the nervous system is involved and which etiologic categories are to be considered, a series of laboratory tests should be planned. Blood count, urinalysis, chest x-ray and lumbar puncture should be done routinely. Studies of the cerebrospinal fluid will reveal much information; the color, serology, cytology, sugar, total protein, and globulin content of the fluid should be ascertained. Other laboratory examinations such as electrical recordings of brain nerve or muscle, and neuroradiologic procedures must be performed as indicated by the anatomic and etiologic classification.

# Diagnostic Aids in the Mental and Aphasic Status

MORRIS B. BENDER, M.D.

*New York, N.Y.*

One of the most commonly neglected tests in the practice of medicine and indeed neurology is that of mental functions. During the past decade there has been an increase in the number of elderly people and among them many have impairment of mental function. Often these defects are taken for granted, and there is no systematic attempt to test these subjects because the standard mental and aphasic status is lengthy and involved. Therefore we propose a brief, simple examination which may be applied in the office or at the bedside.

In our department the bedside mental examination evaluates the following: 1. General Information 2. Orientation 3. Memory 4. Naming of objects and body parts. 5. Right-left orientation and mimicry 6. Simple Calculations and Spelling 7. Reversals and 8. The Face-Hand Test. Almost all of the tests require ability to verbalize and some cooperation by the patient. None is applicable in the very confused or semistuporous patient. Spontaneous speech can be evaluated while the patient gives the history or answers simple questions. During the interview gross difficulties in thinking and communication such as apathy, delayed responses, confusion, incoherence or groping for words may be uncovered.

## General Information

The term "general information" is the general knowledge which should be possessed by most people, such as the name of the President or Vice President of the United States, the governor of the state, number of pennies or nickels in one dollar or eggs in one dozen. Gross and repeated errors indicate serious impairment of function. There are any number of comparable questions including current events which might be used but evaluation may be difficult. The education level should be determined and taken into account during this part of the examination.

## Orientation

In tests for orientation the patient should know the year and even the month. An error suggests impairment of brain function. If the patient cannot recall the correct day, it is not necessarily significant. Confusion as to time of day, such as between night and day, is a severe deficit. The patient is expected to recognize the place in which he is located and the name of the interrogator, especially after there has been a previous introduction of the examiner.

## Memory

Evaluation of memory actually overlaps many other test areas. Examination of recent memory may include recalling the examiner's name, remembering questions during the interview, naming members of the family, and, in older

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patients, the names of grandchildren. Inability to recall names of familiar people or dear relatives, especially grandchildren, indicates severe impairment of mental function. The patient may forget the location of objects, familiar addresses and telephone numbers, performance of routine tasks, or significant events in daily life. Errors in any of the above tests signify brain dysfunction. One simple but useful question is: Where were you last night? The latter may reveal confabulation, *e.g.*, the patient stating he was at home instead of at the hospital.

### **Naming of Objects**

Often the patient complains of inability to recall the names of objects. The inability to name or the misnaming of objects may be an early sign of a localized lesion in the dominant temporal lobe. The defect in naming may be apparent from the history or from spontaneous conversation. An inability to name such common objects as necktie, shoe, or clock by one who has no apparent gross mental deficits is strongly suspicious of aphasia or a localized lesion in the dominant side of the brain.

An evaluation of language function can be made during the taking of the history or during the performance of the physical examination. The distinction between a pure language dysfunction or aphasia and a general defect in mental function is often difficult or impossible. The importance of this distinction lies in the fact that the organic mental syndrome signifies general or diffuse brain dysfunction while isolated aphasia signifies dysfunction of the dominant hemisphere. The difficulty is that the two disorders are usually coexistent. In both, defects in memory and in calculations are common so that differentiation must depend on evaluation of other functions.

Naming and identification of body parts on the person and the examiner should be tested routinely. Inability to identify such body parts as wrist, elbow or knee is distinct evidence of brain dysfunction. This may occur in aphasia or in cases of severe impairment of mental function. Many of these patients may show confusion in identifying parts on the right and left side of the body.

### **Left-Right Commands and Mimicry**

The subject should be tested with single and complicated commands involving crossing from left to right or vice versa. Simple commands such as, "open your mouth," "close your eyes," or "raise your hand" should be issued. Right-left orientation is tested with the command, "place the right hand on the left ear" or some other similar task.

Another function which should be tested is the ability to mimic. Instruct the subject to imitate exactly the following movements made by the examiner: (a) stroke the right face with the right hand, (b) stroke the left face with the left hand and (c) stroke the right face with the left hand. The patient with diffuse encephalopathy watches and imitates the first two performances *pari passu* with the examiner's movements of the hands. However, in the third test there

is no crossing of the midline; instead, the patient rubs the face on the same side, either the right face with the right hand or left face with the left hand. Repeated inability to cross the midline from one side to the other in these tasks may be considered a defect in brain function.

### **Calculations, Spelling, Reading and Writing**

Calculation is tested by figuring meaningful quantities such as how many nickels in one dollar and how many dollars in sixty nickels. If the answer is incorrect, a simpler task—how many pennies in one dollar—should be tried. Addition and subtraction of the one or two digit numbers may be of some value. For instance, calculation of  $94 + 19$  or  $94 - 19$  should be achieved by the high school graduate. As in all mental testing, mathematical problems should be of graded difficulty. Addition of one and two digit numbers and then subtraction of the same number is sufficient for routine purposes. Calculation problems using money or specific items should be tried when there are errors with digits.

Reading is tested with large print, *e.g.*, magazine or newspaper headlines. Spelling tests should include three to five letter, simple, common words, *e.g.*, eat, hand, or world. Persistent inability to recite the alphabet by a high school graduate indicates brain dysfunction. Writing and copying are tested by writing the name or other items, writing to dictation or by copying simple and complex items but such tests are too time consuming and depend on motor performances. They might be used to demonstrate aphasia.

### **Reversals**

One of the most reliable and simple tests of mental function is the ability to reverse the order of sequence such as in counting numbers, spelling words, reciting the days of the week or the months of the year. Most patients with severe mental dysfunction can count from 1 to 10 and even in reverse from 10 to 1. Persistent inability to count backwards from 20 to 1, particularly between 13 and 10, may occur in patients with aphasia.

Another simple routine task is to spell words in reverse. This is a rapid and informative test. The inability to reverse the letter sequence of **WORLD** is a very sensitive indicator of dysfunction and may be the first or only sign of dysfunction. The indication is even greater when **CAT** cannot be spelled correctly backwards. The patient may have no difficulty in spelling long and complicated words but when asked to spell a three or four letter word in reverse there may be gross errors, uncertainty or inability to proceed beyond one or two letters. Good test words for spelling and reversal are: **CAT**, **DOG**, **HAND**, **WORLD**, **HOUSE**, **TABLE**, **CHAIR**, **HOSPITAL** and **PICTURE**. **WORLD** in particular is an excellent test word, neither too hard nor too easy, it serves as a handy initial test word for all levels of education. **HOSPITAL** is another good test word, but this should be given to patients with a high school or college education. For those who cannot spell or do not speak English, the task is changed to reciting days of the week or months of the year in their native tongue. The patient is asked to recite the sequence, *e.g.*, days of the week, in forward and then reverse order. Often the concept of reversals is not grasped at first and the examiner must give an



example by saying "Sunday, Saturday." Disturbance in the performance of simpler reversals is a very reliable sign of mental or language dysfunction. Inability to spell CAT or HAND in reverse in a patient who otherwise shows no gross impairment of thinking or of communication is a reliable and significant sign of brain dysfunction. The sign which was observed in more than 1,500 cases appears to be more valuable than the Babinski response.

### Face-Hand Test

This simple test which consists of reporting the perception of tactile (rubbing) stimuli simultaneously applied to the patient's face and hand has been shown to be of value in examinations for brain dysfunction (1). When the patient errs by failing to report or mislocalizes one stimulus, it is a sign of cerebral dysfunction. This is known as a "positive" face-hand test. As a rule, the error is in the perception of the hand stimulus; either it is not reported or it is mislocalized to the face. The persistence of these errors on either side, even after the patient is informed that two stimuli are being applied, is a distinct sign of brain dysfunction. Such patients do not learn nor can they remember that two stimuli are being applied. Normal children under the age of six years may err even after the tenth trial. However, once the normal child learns that there are two stimuli subsequent responses are correct. In severe cases errors persist even when the patient is permitted to view the application of both stimuli. A positive face-hand test is frequently found in the aged and may be considered as one of the perceptual manifestations of aging. The older the subject the greater the incidence of errors (2). A positive face-hand test, unless it is present with the subject's eyes open, may occur in apparently normal old people. These subjects may manifest other impairment in mental functions, such as defects in memory or in reversals.

A similar test which may reveal much more serious brain dysfunction is one which involves interaction between visual and tactile functions (3). The patient with eyes open is requested to report the perception of the following two stimuli (a) tactile, *e.g.*, rubbing of the patient's right hand and (b) visual, which consists of the patient looking at a rubbing motion over the examiner's right face. In this test situation only the patients with severe brain dysfunction err in the response reporting the perception of a tactile stimulus over their own face. The visual stimulus is misinterpreted as being tactile while the tactile stimulus at the hand may be mislocalized or not perceived at all.

### General Comment

Of all the foregoing tests used in eliciting mental dysfunction, the task of reversing serial order, such as spelling the words CAT, HAND or WORLD backward is the most valuable and easiest to perform. This simple test which can be applied readily in the office or at the bedside should be used routinely to elicit mental dysfunction, just as stroking the plantar surface of the foot is used for the elicitation of involvement of "the pyramidal tracts". An inability to spell CAT backward is as significant and even a more reliable sign of brain dysfunction than is a Babinski response. All other tests for mental function are

less simple and, unless there are gross errors in performance, are more difficult to evaluate.

### SUMMARY

Many simple tests for mental dysfunction were described. Each contributes toward evaluation of mental status. Of all, the simplest and most reliable test is the spelling of simple words; CAT, HAND, or WORLD backward.

### REFERENCES

1. Fink, M., Green, M., and Bender, M. B.: The Face-Hand Test as a Diagnostic Sign of Organic Mental Syndrome. *Neurology*, **2**: 46, 1952.
2. Bender, M. B., Green, M., and Fink, M.: Patterns of Perceptual Organization with Simultaneous Stimuli. *A.M.A. Arch. Neurol. & Psychiat.* **72**: 233, 1954.
3. Nathanson, M., and Anderson, P. J.: Ipsilateral Versus Contralateral Performance in Normal Subjects and Patients with Diffuse Cerebral Disease. *Tr. Am. Neurol. Ass.* **84**: 192, 1959.

# The Evaluation of Some Aspects of Vision

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This section describes methods which can produce a rapid and adequate description of the patient's vision with simple apparatus easily taken to the bedside. In our experience these "gross" techniques are not only useful, but in some respects superior to ophthalmologic methods using technical equipment. They will detect early changes in the visual fields and, for all practical purposes, separate normal from abnormal subjects. The physician who uses these techniques routinely will acquire enough experience to have confidence that his results are reliable.

## Visual Fields

**Perimetry.** Conventional perimetry has obvious advantages: 1. It gives an accurate outline of the visual field and the relative size of the field for various sizes and colors of targets, 2. it is unsurpassed for delineating small peripheral defects and scotomas of odd shapes, 3. serial determinations can detect small variations. However, it lacks the convenience of simple, portable equipment and often requires cooperation for long periods of time, which may be impossible for neurological patients. More importantly, perimetry is not ordinarily part of a routine examination. Since many visual field defects are discovered unexpectedly, a careful evaluation of vision should become "routine."

The bedside testing of vision is based upon some of the following factors: 1. figure-ground discrimination, 2. the dependence of the defect upon the method of testing, and 3. double simultaneous stimulation.

**Figure-Ground Discrimination.** Figure-ground discrimination is involved in all sensation including vision. We make such discriminations constantly—the newspaper headline gains our attention because it stands out by virtue of its size and boldness. We can ignore it, however, when we read the story—thus, figure and ground constantly change places. In defective visual fields this discrimination is blurred and properly designed tests will detect the abnormality.

**Method of Testing.** If the nature of the stimulus is changed the size and shape of the visual field will seem to change—a patient may see a moving hand in all parts of the field and if tested only in this way appear to have normal fields. However, if the stimulus is a red match tip, he may see it on only one side and not on the other; therefore, with this method there is a demonstrable field defect.

Certain types of stimuli are more difficult to recognize than others. Motion is easiest to perceive, form recognition is next, and color is the most difficult.

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Thus, the size of the field will be the largest (about  $180^\circ$  on the temporal side) if tested with hand motion or large white objects, smaller for the identification of objects, and smallest when the test objects are small, colored circles. Disease brings out this pattern since the first function to be lost is color identification whereas it is the last to recover when the patient improves. On the other hand, recognition of motion is the most resistant to disease processes and, as would be expected, is the first faculty to recover.

**Double Simultaneous Stimulation.** If two targets are presented at the same time, the target in an area of defective vision may be lost or seem to change its characteristics whereas if presented alone it will be reported correctly.

**Location of Intracranial Lesions.** Visual field defects are generally accurate indicators of the location of intracranial lesions. Almost without exception, a homonymous field defect points to the opposite cerebral hemisphere in its posterior two-thirds. Even the "classical" indicators of lesions on one side of the brain or the other, such as a Babinski sign or a hemiparesis, may be misleading. As a rule, a left Babinski sign is found in right cerebral lesions but in some cases it may occur in a left cerebral lesion. This is rarely the case with visual field defects; a left homonymous hemianopia is a reliable indication of a right cerebral lesion and its visual radiation (that is, that portion of the visual pathway between the lateral geniculate body and the occipital lobe, with its ramifications in the temporal and parietal subcortical regions).

Although many textbooks stress the fact that lesions of the optic tract (between the chiasm and the lateral geniculate body) also result in homonymous hemianopia and emphasize methods of differentiating them by the characteristics of the visual field defect, such lesions are in fact extremely rare and for all practical purposes may be ignored.

Bitemporal field defects are highly characteristic of lesions of the optic chiasm, again with very few exceptions. Central scotomas indicate optic nerve disease.

Peculiarly shaped scotomas, sector defects and other rarities are uncommon in neurologic lesions and occur predominantly in ocular pathology.

## Methods

### Observations by the Patient

The use of conventional eye charts is impractical at the bedside. However, the patient's report of what he sees around him or how he reads can be extremely informative. He may, for example, ignore everything on one side. People who enter and leave the room on that side may be ignored. This phenomenon, which is always associated with a homonymous field defect and mental changes, is called "hemispacial agnosia" (there are also other names for it). It is generally associated with inability to draw complete figures (one side is omitted) and inattention to other types of stimuli (sounds or skin perceptions) on that side.

The patient often indicates his own field defect quite accurately in describing the examiner's face. For example, if he sees the nose but not the eye or ear on the same side, there is a homonymous defect with relative sparing of central vision. As a patient scans a printed page or an eye chart, consistent omissions on one side or the other are indicative of abnormality.

Note that in the foregoing, as well as in the tests to be described subsequently, it is necessary to test each eye separately.

### Testing by the Examiner

**Double Simultaneous Stimulation.** The value of using double simultaneous stimulation in tests for sensory functions is well known. In brief, a single stimulus (such as a touch, a sound or an object to be seen) may be reported correctly even if it is in a defective area. However, the patient may fail to perceive it if another stimulus is given at the same time in a normal area. In the case of visual field testing there is actually a third stimulus, the fixation point.

Most field defects will be disclosed by this method. Moving fingers are brought in from the extremes of the field on either side and the patient is asked to report what he sees. The fingers should be placed in diagonally opposite quadrants (upper nasal and lower temporal, for example) in order to detect quadrant defects and to avoid the physiological blind spot in the temporal field. A positive test consists of the following responses:

- 1) Report of seeing only one of the two fingers ("extinction").
- 2) Report of seeing the two fingers, though unable to localize one of them by pointing to it.
- 3) Report that one finger looks blurred or indefinite in some way.

The results of this test can be influenced by uneven illumination so that, if possible, the light should come from behind the subject. In addition, the wall or other background behind the examiner should be uniform. If these conditions are not met the examiner and subject should change places and the test repeated.

If this test is negative, more complicated testing should be done, again using one target in each of two fields:

- 1) Two dissimilar objects (such as a safety pin and a coin) are exposed simultaneously and the patient is asked to identify what he sees.
- 2) The patient is asked to count fingers on each of the examiner's hands.
- 3) The most useful test objects are ordinary paper or wooden matches with red or green colored heads (Fig. 1). As previously mentioned, color recognition is lost early in lesions of the visual pathways: in this test 3-4 mm colored targets are exposed simultaneously. The patient is asked to fixate the examiner's nose and the examiner holds one match on either cheek. (Remember that the normal field for this size of colored object is quite small.) A defect is disclosed when he fails to see one target or reports it as white, gray or less intensely colored than the other. The test is then repeated with one match directly on the examiner's nose and the other on his cheek. Central scotomas will be



detected readily if the patient fails to see the match on the nose yet sees the other one. This is an extremely delicate test and it misses a defect only rarely.

Increasing experience with these methods confirms certain theories that have been largely unexplored except in experimental situations. For example, the terms "macular-sparing" and "macular-splitting" are only relative distinctions. Using large white objects or finger motion, the macular, or central portion of the field may be unaffected. However, when colored matches are used the field defect may extend all the way to the midline.

**Threatening Gestures.** In stuporous or aphasic patients, a popular method of examination is to observe the response to threatening gestures presented from one side or the other. These can be a moving hand brought rapidly towards

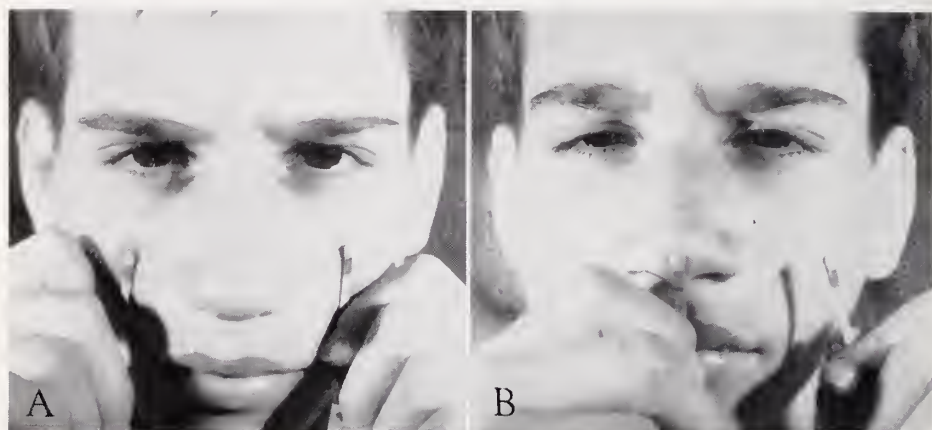


FIG. 1. Method of detecting visual field defects using paper matches with colored heads. The examiner holds the matches as shown and patient is asked to report what he sees while fixing on the examiner's nose. A: With the matches on the two cheeks, one or the other may be ignored, reported as not as bright as the other, or as not having any color at all. Any of these responses indicates a defect in the corresponding half-field. B: With the match-heads as shown, the match on the nose may be incorrectly reported or not seen at all, indicating a central field defect.

the eyes, the point of a pencil brought close to the cornea, etc. The response is blinking, wincing or withdrawal on one side and not on the other. In our experience this method is unreliable for detecting homonymous field defects. If the response is consistently different on the two sides, it can indicate dysfunction in one cerebral hemisphere, but not necessarily affecting the visual system.

**Hysteria.** Many visual field defects have been described in hysteria, which is a much more common condition than is generally assumed. One example is the "gun-barrel" field in which the absolute size of the field at one foot is the same as at, say, six feet. The "spiral" field becomes smaller and smaller (or larger and larger) as testing is repeated. Unlike the visual field defects in organic disease the hysterical field does not vary consistently with the size and character of the test object. The field for match heads, object recognition and moving fingers will be of the same size and shape, which is impossible in

lesions of the visual pathways. If there is a difference between the sides it is generally one eye that is defective rather than the homonymous fields of both eyes.

**Extinction.** As already mentioned, extinction is the failure to see or report one or two simultaneously exposed test objects. When it occurs in only one area or in homonymous half-fields it is of pathologic significance. However, extinction is also an everyday phenomenon. We pick out significant parts of a picture and ignore the others; we select a single voice in a noisy room; the magician uses sleight-of-hand to produce visual extinction at will; in the tactile sphere it is used by pickpockets.

**Completion.** There is one other phenomenon, the opposite of extinction, which also has everyday counterparts and may be seen in defective portions of the visual field. It is called completion and can be demonstrated at the bedside. If a large letter C is exposed to a patient with a right-sided field defect, the gap in the circle may be "completed," and the letter reported as an O. In central scotomas, the incomplete figure  $\times$  may be reported as a perfect X.

**Adaptation.** Up to now, the testing has emphasized the *spatial* characteristics of visual fields. However, there are also *temporal* aspects, an example of which is adaptation. The apparent disappearance of unpleasant odors after a few minutes is a familiar instance of adaptation. A pin prick on the hand of a patient with a hemisensory deficit may be initially perceived but seems to disappear after a few seconds. Using double simultaneous stimulation the phenomenon can be demonstrated in visual fields. Again, the match heads demonstrate this most easily—that is, one match head may seem to disappear or grow indistinct after a few seconds when it is in a defective field.

**Adaptation Time.** As in other sensory modalities, adaptation time is reduced in abnormal fields. That is, a target in a defective area will seem to fade or disappear more quickly than in an intact portion of the field. This difference is easily brought out by exposing two targets simultaneously. Even though both are perceived, only one will remain unchanged after 5 or 10 seconds. The patient may report disappearance, fading of color, or blurring of the outlines of the object in an abnormal area. Again, useful targets are match heads, safety pins, and coins. Rapid adaptation would seem to be the opposite of the phenomenon observed in rapid presentation of targets, in which the object is not seen if exposure time is short, but occurs after the object remains for a few seconds. Actually, both may occur in the same field.

### Testing for Enlarged Blind Spots

Even using perimetry, measurement of the physiological blind spots (which is a measure of the size of the optic nerve head) is difficult. Nonetheless, enlargement of the blind spots may sometimes be detected using bedside methods. The match heads are brought in slowly through the temporal fields of each eye and a scotoma may appear which is large in extent and therefore easy to elicit. A normal blind spot will be hard to detect in this way, so that an

obvious defect indicates an abnormality. If it appears in both eyes, it may signify enlargement of the blind spots, although the findings will be the same in bitemporal scotomas due to chiasmal lesions. Enlargement of the blind spot is encountered in papilledema and certain nonpathologic conditions such as pseudo-papilledema, gliosis of the optic papilla, drüsen; in fact, anything that causes the optic disk to be larger than normal. Two things should be emphasized: 1) Detecting enlarged blind spots is difficult and requires a great deal of experience, and 2) Enlargement of the blind spots does not always signify papilledema.

### Pseudo-Isochromatic Plates

A test that utilizes most of the principles of vision already described is one in which the test objects are the pseudo-isochromatic plates. These are the familiar number-plates in general use for detecting color-blindness. They consist of white cards, 4-6" square, covered with colored circles of various sizes. A central digit or pair of digits is distinguished from the background by the fact that it is printed in a different color from the circles of the background. Care has been taken so that the saturation and intensity of the colors of the figure and background are the same and that only hue distinguishes them. (On one card of the series designed to detect simulated color-blindness a colored figure appears in a background of neutral gray circles [Fig. 2].)

The usefulness of this test in neurologic disorders was discovered while working with patients who had the syndrome of hemispatial agnosia. In this condition there is a homonymous field defect and mental changes. The patients ignored the digit on the side of the defective visual field. Thus, a patient with a left homonymous field defect reported a 74 as 4, 12, as 2, or in the case of single digits such as 8, split the figure and reported 3. Since then it was found that many visual field abnormalities could be detected by means of the pseudo-isochromatic plates.

The test is administered without strict conditions of any kind. The patient is shown a card and asked what he sees. If he requires corrective lenses for reading he must wear them. All the cards are shown and responses recorded. Each eye is tested separately.

As in other tests, a consistent pattern of errors is significant. The errors may consist of the patient's failure to report digits, reporting them incorrectly, repeatedly hesitating, or vacillating in his reports of one or the other.

If the patient does not make errors under these conditions, the series of cards is shown again using limited exposure times. A card is exposed for a second or so; if there is no response the time is lengthened until some answer is given and then this exposure time is used for all succeeding cards. (Although this is a form of tachistoscropy, widely used in the laboratory, no specific times are used or recommended. As in the other tests described previously, imposition of rigid conditions of testing actually *reduces* the value of these bedside procedures.)

In spite of the complex nature of the visual discrimination involved here

(from a physiologic point of view) the test can be interpreted in many (but not all) confused, aphasic, or otherwise "uncooperative" patients, including children who are too young to identify numbers. We have been surprised repeatedly at the cooperation displayed on this test by aphasics and others. If no verbal response is obtained we ask the patient to point to what he sees; if he points to only the right-or-left-sided digits the same interpretation can be made as though he gave the response verbally.

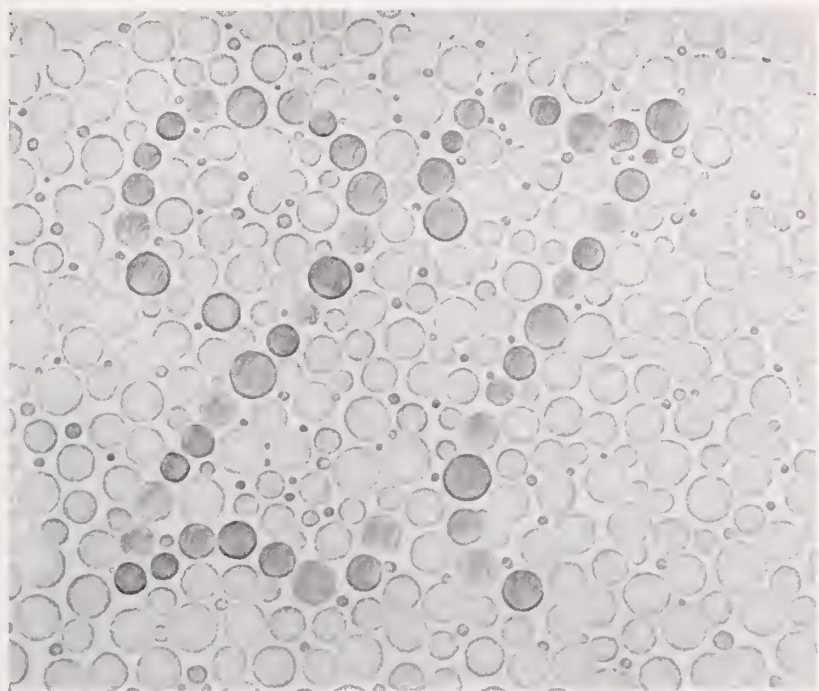


FIG. 2. One of the Pseudo-Isochromatic Plates. Errors in reporting the left-hand digit (such responses as 7 or 37) or the right-hand digit (such responses as 2 or 21), if consistent on a series of cards similar to this one, indicate defects in the corresponding half of the visual field. Failure to report both digits correctly (especially when the test is done perfectly with the other eye) indicates a central scotoma or other central field defect. (The original plate was retouched for purposes of black-and-white reproduction.)

The *pattern* of errors is interpreted in exactly the same way as in other visual field tests; homonymous errors, bitemporal errors, and errors in only one eye signify dysfunction in the retrochiasmal pathway, optic chiasm or optic nerve respectively.

In spite of the fact that the test was first developed in patients with mental changes (as in hemispatial agnosia), many patients without them make the same errors. In fact, more patients with chiasmal or optic nerve lesions (who usually do not have mental changes) make significant errors than those with defects in the cerebral hemispheres. The greatest factor in the production of errors on this test is the presence of involvement of the central portion of the



visual field. Not all patients with visual field defects make errors using this method, and therefore it cannot be used to *exclude* lesions of the visual pathways.

The results in color blind persons are harder to interpret; however, these subjects can often see a few of the cards and a definite one-sided pattern can only be the result of a field defect. Color blindness restricted to one eye is so rare that it may be ignored.

### SUMMARY

In summary, methods of bedside testing of visual function have been described. These have great practical value to the physician and also illustrate certain principles of normal and abnormal visual function. Although some of them are so simple that their use may appear naive and their description superfluous, they give accurate and unequivocal information about the patient's vision. Their simplicity, furthermore, permits the physician to gain experience in large numbers of cases and frees him from dependence on the ophthalmologist for an essential part of the neurological examination.



# Modifications of the Sensory Examination

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The sensory status can be evaluated in every patient. There is no problem when the subject is alert and can verbally describe the nature, quality, and location of the sensory experience. The alert patient with a lesion in the nervous system often gives an accurate and detailed account of the impaired sensation. In the confused and aphasic patient the sensory examination is more difficult; one must depend partly on the patient's verbal response and partly on the emotional reaction. In semistupor the sensory function can be evaluated to some degree by the gross motor reactions to noxious sensory stimuli; there may be wincing or the withdrawal of a limb more on one side of the body. In the comatose state the sensory stimulus response may consist of purely reflex motor reactions. Here it may be impossible to determine whether lack of a response is due to a sensory or motor loss.

In the alert subject pain (pin prick), temperature (cold metal), tactile (light touch with a finger), vibration (128 tuning fork) and position sense (in fingers and toes) are tested. These are routine tests and do not need comment. These modalities are tested by the standard method of application of a single stimulus for a brief moment. However, modification of the technique may disclose defects which ordinary examination may fail to evoke.

## Tests for Appreciation of Vibration Position and Two Point Discrimination

Appreciation of vibration is usually tested by placing a vibrating fork over bony prominences. If the patient indicates there is vibration it is difficult to determine whether there is a decrease in this modality. Partial impairment of this sensory function can be detected by testing over soft tissues, *e.g.*, abdomen, thighs, calves. A sensory level can be ascertained over the abdomen (1). Impairment in the fingers can be detected by simultaneous comparison of the patient's and examiner's perception of vibration. If the examiner places his own finger under that of the patient the vibration will be transmitted to the examiner. After a few seconds as the vibrations diminish in intensity, the patient may state that there is no longer vibration, whereas the examiner may continue to appreciate it. Thus testing each finger in this manner may reveal a reduced though not absent vibration and it will help to detect a lesion in the nervous system much earlier. The sense of position is usually tested in fingers and toes but when there are gross defects impairment of sense of movement and position may be found in the larger joints such as at wrist, elbow, ankle, or knee. These are simple tests and when the response is faulty it means gross impairment of function. As for two point discriminations, the tests are made in tips of fingers

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and occasionally in lips and tongue. It is rarely tested in the toes chiefly because the distance between the two points when discrimination is possible is bigger than the toes tested. To obviate this, the points should be applied across three or more toes (*e.g.* first and third).

### **Sensory Adaptation**

In tests for pain or other modalities the ordinary method may evoke no abnormalities. A single brief pin prick stimulus may be reported as normal. Also when the stimulus is applied continuously the normal subject will continue to feel the pin even after a period of 100 seconds. However, beyond this interval the sensation will often fade and disappear. The time elapsed until disappearance is known as the sensory adaptation time which may be as long as 3 minutes (2).

The test for sensory adaptation is simple. The stimulus should be applied with the patient's eyes closed and for a period of not more than 15 seconds. If the adaptation period is more the clinical significance is little, if less such as within 5 seconds one must consider the sensory area as malfunctioning. To confirm this finding one should always test other areas of the sensory field. The test may be performed with simultaneous application of stimuli on two sides of the body. Under such conditions the adaptation time may be further reduced to one or two seconds, making the difference in sensibility more apparent. In some cases of sensory disorder the adaptation time may be drastically reduced. The patient with a right parietal lobe lesion may report a disappearance of a sensation after 2-5 seconds of continual application of a pin prick stimulus on the left hand or anywhere on the left side of the body. Thus a patient with a two month history of headache had no gross abnormalities on routine neurologic examination but repeated tests for sensory adaptation disclosed markedly reduced adaptation time in the left hand and to a lesser degree on the left side of the body. With this significant sensory finding angiography was performed and a right subdural hematoma was discovered.

### **Tests with Double Simultaneous Stimulation**

As mentioned in tests for adaptation time, bilateral simultaneous stimulation may evoke a deficit which is much greater than on unilateral single stimulation. The sensory phenomenon which occurs on simultaneous stimulation has been known for thousands of years. The art of pickpocketing depends on the principle of interaction between two simultaneously applied stimuli. In patients with lesions of the nervous system sensory defects can often be uncovered with the double technique (3). The method consists of pin prick stimuli simultaneously applied to the right and left hand or other homologous parts. In a patient with a lesion in the right side of the brain the patient will report the percept in each hand without difference in quality when the stimuli are applied successively. However, when the two hands are tested simultaneously only the right percept is reported; the left is not perceived. Painful, thermal, tactile, stereognostic, and other sensory functions may thus be tested and deficits un-

covered whereas routine stimulation may show "normal" responses. The method of bilateral or double simultaneous stimulation is well established and may be used in tests of other sensations such as vision and hearing.

### **Sensory Status in Patients with Confusion, Aphasia, Stupor, or Coma**

The method of simultaneous stimulation can also be used to elicit sensory deficits in the confused or aphasic patients. Consistent sensory deficits in the mentally confused may not be apparent by conventional methods of testing but may with double simultaneous stimulation. Unilateral defects in somatosensory functions, vision, and hearing may be elicited. A patient with severe mental deficits with apparently normal motor functions showed no impairment of vision, hearing, or pin prick sensibility when examined by the conventional method of single unilateral stimulation. The same patient failed to perceive any of the above modalities on the left side when tested with bilateral simultaneous stimulations. These sensory deficits were the only manifestations of a localized disturbance.

In the severely aphasic patient one must observe the motor and emotional reaction. Thus with single pin prick stimulation applied to the right or left hand the withdrawal may appear to be equal on both sides. However with bilateral simultaneous stimulation in the same areas the act of withdrawal may occur only with the left hand.

In stuporous patients, moderately noxious pin prick stimuli across the forehead or in the limbs should be used and response can be judged by facial expression or limb withdrawal. However, unless there is a consistent difference in the response on the two sides no conclusion can be drawn as to implication of a cutaneous sensory field.

In the comatose patient such as in acute stroke or intraventricular bleeding, sensory examination is impractical. A stuporous or comatose patient with an acute spastic left hemiplegia may respond to noxious painful stimuli with a patterned movement of the paralyzed limb. This does not exclude involvement of sensation. These are segmental response and usually indicate a poor prognosis particularly if the segmental response is bilateral. Pinching or pin prick stimuli on the skin across the chest wall may evoke an ipsilateral extensor movement at the elbow, overpronation and flexion at wrist and marked clenching of the hand. Stimulation in the pubic or lower abdomen area may cause ipsilateral extensor movement at the knee, as well as plantar flexion and inversion of the foot. When these responses are unilateral they signify damage in the opposite cerebrum; they also indicate that recovery of useful function in these limbs is not good.

### **SUMMARY**

Besides the routine sensory examination tests for appreciation of vibration, sensory adaptation time and method of double simultaneous stimulation are described. These simple tests can reveal deficits not elicited by conventional techniques.

## REFERENCES

1. Bergman, P. S.: Cutaneous Vibration Perception in Neurologic Disease. *Tr. Am. Neurol. Ass.*, 87: 50, 1962.
2. Bender, M. B.: Changes in Sensory Adaptation Time and After-sensation as Symptoms of Parietal Lobe Lesion. *Arch. Neurol. & Psychiat.*, 55: 299, 1946.
3. Bender, M. B.: Disorders in Perception (with Particular Reference to Phenomena of Extinction and Displacement), Springfield, Ill: Chas. C. Thomas, 1952.

# **Motor and Reflex Testing**

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Conventional methods of testing motor function include a routinized systematic evaluation of power at each joint regardless of the apparent anatomic source of weakness. In contrast, this communication will attempt to deal with patterns of power testing because there are differing patterns of power loss depending upon whether a lesion is central (brain, brainstem, spinal cord) or peripheral. Deficit in strength in a central lesion may be said to be a disorder of movement whereas in a peripheral lesion it is a disorder of muscle. Therefore, emphasis should be placed upon certain aspects of the examination in each situation. For example, in a cerebral lesion if certain key movements are weak, testing all movements will add little to the meaningful data. However, in a suspected nerve root lesion, testing all muscles supplied by the root in question is indicated.

## **Observations**

The following spontaneous activities should be observed: 1) Facial movement in conversation, smiling, and blinking for evidence of sagging of the angle of the mouth and greater mobility of the opposite side of the face. The side which sags in repose may show paradoxically greater mobility in smiling but testing against resistance should disclose the actual side of the weakness. 2) Tremor, choreo-athetotic grimacing, dystonic trunk and leg movements, decreased arm swing, leg circumduction, spasticity, dragging, or foot drop (slapping the floor) in walking. 3) Awkward arm movement or incoordination as the patient attempts to light a cigarette. 4) Bizarre attitudes or levitation of an arm or leg. 5) Synkinesias or movements related to contractions in muscles other than those being tested. Contraction of circumoral muscles when the eye is shut or vice versa may indicate a peripheral facial lesion. Similarly, in a central lesion, an arm or hand may move automatically when alternating leg movements or power are being tested and vice versa.

When the patient is observed in bed, failure to spontaneously move an arm and/or leg unilaterally points to a central motor problem which is not explained on the basis of weakness alone.

## **Examinations**

### ***General Principles***

Tests of power depend upon the examiner's perception. The least power needed to move a part or to resist the patient's attempt at movement should be determined. Generally, it is easier to determine the presence of weakness by permitting the patient no initial advantage. Thus, the patient usually should



not be permitted to fix a given joint because his advantage becomes too great. Similarly, hand or foot dorsiflexion weakness is more easily demonstrated when the patient starts from the flaccid or rest position rather than the extensor position. This approach is more practical for testing movement of large or long muscles. In testing digital power, however, the examiner should permit the patient maximum advantage.

### *The Pattern of Central Motor Defects*

The pattern of central motor deficit (cerebral hemisphere to the high brain-stem region) is unilateral weakness of: facial movement, shoulder elevation, thumb and small finger abduction, elbow and wrist extension, thigh flexion on hip, and toe and foot dorsiflexion. These movement defects predominate in cerebral hemisphere and high brainstem lesions. Facial movement is usually affected the least.

**Facial Muscles.** Eye and mouth closure and platysma activity are the most sensitive tests of facial power. The patient closes his eyes with maximum force and the examiner attempts to open each with a finger, or holds the upper lid with the finger during closure, or stimulates the cornea and assesses the force of the motor response while the upper lid is held. A wider palpebral fissure suggests weakness of eye closure on that side as does decrease in lid excursion in spontaneous blinking on one side and failure to close the eye completely in sleep. As a test of mouth closure, the patient apposes his lips, not his teeth, with maximum force in preventing the examiner from opening his mouth. The examiner then pulls the upper lip upward on each side and the lower lip downward, in sequence. Gentle pressure may be exerted on the platysma with the other hand to determine its tone because this movement is often present synkinetically. Forceful neck flexion against resistance applied to the under surface of the chin will also bring the platysma into play. To test for decreased tone of the nasolabial fold, the examiner gently pulls upward on the fold as the patient forcibly closes his eyes. These methods are more sensitive than devices such as whistling, puffing the cheeks, wrinkling the forehead, or showing the teeth.

**Fingers.** Radial abduction of the thumb is probably the most sensitive test for weakness of central origin. The patient extends his fingers and raises his thumb forcefully at a right angle to the radial border of the arm and fingers. The examiner attempts to push the thumb downward toward the index finger with his own index finger placed at the level of the interphalangeal joint. The approach should be standardized for each hand, either from the palmar or dorsal side. A less sensitive variation of this test is to have the patient press thumb against index finger, tip to tip; the examiner attempts to pull his index finger through this "ring" or to separate the two digits. Abduction of the small finger is also a sensitive movement. The fingers are spread as strongly as possible and the examiner straddles the index and small fingers at the distal interphalangeal joints with his thumb and middle finger and then gently forces the fingers together.

**Elbow and Shoulder.** Elbow extension is tested by having the patient push anteriorly against the examiner's thumb-index finger web, with the patient's wrist cradled in the web. The patient's elbow may start at  $45^{\circ}$  flexion from the shoulder, closer to the shoulder, and at  $90^{\circ}$  of elbow flexion. Shoulder elevation is tested singly and doubly with the examiner's hand on the patient's shoulder in a crossed epaulet position. Starting from a resting position, the shoulders are shrugged forcibly in a single movement. Abduction of the arm at the shoulder may be affected in a central weakness pattern.

**Toe and Foot.** Toe dorsiflexion weakness appears before foot weakness, and small toe weakness precedes that of the great toe. Therefore, the patient is asked to dorsiflex all his toes and the examiner attempts to depress them with the distal parts of his fingers. Resistance of the great toe is tested by hooking the index finger over the dorsal surface of the toe and pulling downward. In contrast, foot dorsiflexion should be tested by having the patient start from the plantar flexed rest position, while the examiner's palm is placed on the dorsum of the foot in resistance.

In general, the writer has found it easier and more effective to test the movements described for the upper extremities and face with the patient in the sitting position on a bed or examining table. Pronation, posturing, drift in an upward or downward direction and trunk deviation should be noted when the arms are held outstretched and eyes closed.

### **Associated Movement Defects**

Since weakness of central origin is a movement deficit, other disturbances in movement are to be expected. Indeed, they are among the most valuable corroborative signs. It should be kept in mind that overlap in phenomenology is unavoidable. Thus, hand awkwardness in performing a movement may be the result of involvement of one of several different systems; cerebral, so-called basal ganglia, cerebellar, or proprioceptive.

### **Rapid and Fine Movements**

For testing rapid and fine movements the patient is requested to open and close the fist rapidly; the speed, precision and local control are noted. Careful notation of the behavior of the distal phalanx of the thumb is important. In this maneuver it should flex along with other flexor movements. If it remains straightened, or after several movements, straightens and does not flex again, there is a defect. The opening and closing of the fist should be done with the hands relatively outstretched in front of the patient, palmar surface down. The patient is also asked to rotate his outstretched arms and hands with the limb at  $180^{\circ}$  throughout. Disorganization of this movement indicates the presence of a movement deficit as does disorganization of rapidly patting the thighs, alternating palm up and palm down while sitting. Likewise, the patient is asked to tap his wrist with the first two fingers of the opposite hand (not the thumb) and then to alternately tap with palmar and dorsal surfaces of these fingers. Again, decomposition of the movement indicates a defect. With the

hands outstretched and held relaxed, the patient is asked to wiggle only the index finger upward and downward, without moving the other fingers. Disorganization of this movement is indicated by overflow of the movement to the other fingers. Rapid tapping of the thumb at the interphalangeal joint by the index finger is a useful rapid movement as is the rapid tapping of other fingers in sequence by the thumb sometimes called "piano playing." In these maneuvers, one hand serves as a control but bilateral movement disorders can be present.

When the patient is supine he is asked to tap the examiner's hand rapidly with the sole of his foot or to tap the foot of the bed. Or, when standing he taps the floor repetitively. The basic movement should be one of flexion and extension at the ankle without bringing the more proximal joints into play. Rotational movements may be tested in both situations by having the patient rapidly rotate the foot on the heel while recumbent or to pivot rapidly to and fro on the heel while standing.

Rapid tongue movements may be tested by having the patient move his tongue rapidly from side to side or by rapidly protruding and retracting it.

### **Coordination**

Arm coordination is tested by having the patient, with eyes open, touch the examiner's index finger, which is moved from position to position with his own, or to touch his finger to his nose, or to draw a number in the air. The arm should be extended fully and unsupported at the elbow. Contact should be precise with no associated abnormal movement. Marked defects with eyes closed but not open may indicate that the problem is one of position sense. Minor differences do not carry this connotation.

Leg coordination is tested when the patient touches the examiner's finger with his great toe, places his heel directly on a match book on the opposite patella without dislodging it, places one heel on the opposite knee and moves it directly down the shin to the dorsum of the foot in successive movements, or draws a number in the air with his foot, such as a figure eight.

Gait is tested by walking in tandem, backwards, pacing off from side to side with the feet remaining parallel and stopping suddenly on command. Note whether the movement is promptly checked or whether the patient cannot overcome his inertia in a particular direction. To test station, the patient is asked to stand in tandem with one foot directed forward and then the other and to balance on one leg with the eyes open and closed.

To test for so-called past-pointing the examiner forms a small "V" with his two index fingers which the patient touches repeatedly with eyes open and then closed. Normally, he should be able to touch this point with precision.

For coordination of trunk, the patient sits hands outstretched and eyes closed. The examiner can suddenly thrust his hand against the patient's outstretched arms to see whether balance is immediately restored.

Handwriting disorders may indicate the presence of an organic problem without other evidence. The ability to handle curvilinear movement is most important and decomposes early.

## Muscle Tone

Muscle tone is examined for evidence of increased or decreased resistance. To test neck tone, grasp the chin and subocciput and rock the head to and fro and side to side with the chin directed alternately toward each shoulder. For arm tone, grasp the patient's hand in a handclasp and place the other hand on the biceps, then rotate the forearm and extend the arm at the elbow and flex and extend the hand. Placing one hand on the biceps helps to determine whether cog-wheeling is present. Grasping the wrist and shaking the arms noting the "floppiness" of the passive hand movement is a similar test of resistance. The dangling legs of the seated patient may be thrust backward below the knees and the amount of pendular activity noted. A circumducted or figure eight movement is abnormal. Leg resistance is also tested by grasping the knee and rapidly rotating the leg on the heel of the supine patient. A sliding heel movement, which may also be heard, indicates increased resistance. The leg may be held at the foot with one hand and supported in the popliteal region with the other while ankle, knee, and thigh are alternately flexed and extended. Rotational resistance at the hip may also be determined with this maneuver.

A judgment based on experience is made concerning decreased resistance or excessive "floppiness" of hand or foot. The outstretched hand may suggest that hypotonia is present if the fingers are overextended and the hand assumes a "spooning" posture. The capacity to check a forceful movement should be noted.

Individual muscle responses to direct stimulation include the degree of movement, myotonia, or fasciculations which are determined by striking the muscle belly with fingers or reflex hammer. Myotonia may be elicited when the muscle is contracted voluntarily and then abruptly relaxed. Muscle activity and a cold environment are conducive to eliciting fasciculations. The presence of fasciculations may be seen in central or in peripheral lesions or may have no significance whatever. One usually depends almost exclusively on concomitant signs to determine whether an organic problem exists.

## Adventitious Movements

Adventitious movements include fasciculations, tremor, and choreo-athetodystonic movements. The examiner should be alerted by an abnormal attitude or posture of the limb, by a dipping gait seemingly involving one leg, by overflow of movement to muscles not necessary to perform a task (buttoning or tying a shoe lace), and by movements at a distance such as sudden extensor toe movements when the patient grips the examiner's fingers. A sudden extensor or flinging movement of an arm or hand while the patient walks is significant. A milking movement present during tests of grip is actually an inability to maintain a sustained contraction. During this maneuver, the patient with dyskinesia is often unable to maintain the tongue protruded; it may dart in and out. Overflow movement may be tested by asking the patient to suddenly flip his outstretched hand from the supine to the prone position with the hand parallel to the floor. Overpronation and inability to check the hand at the appropriate point are pathologic signs. A relatively insignificant-appearing phenomenon



such as clenching and opening the fingers inappropriately while walking may serve as an indication that a dyskinesia is present.

### **Fatigue**

Fatigue of a movement may be tested in several ways and for different purposes. When holding the arms or legs elevated before him the patient is tested for drift or pronation. If drift occurs it indicates the presence of neurogenic movement disorder. The second method of testing for fatigue consists of exercising the patient in a particular movement. The primary intent is to determine whether the muscles themselves are diseased. The examiner may request the patient to raise his arms overhead successively in the usual calisthenic type of exercise. When the patient can no longer perform or complains of excessive fatigue, the power in that particular movement should be tested and then retested after several minutes of rest. At the same time, the appearance of muscle weakness elsewhere is noted as the appearance, or worsening, of ptosis. Any muscle or group of muscles suspected of being weak, by history or examination, may be exercised. The application of tests for muscle fatigue is particularly important in suspected myasthenic syndromes.

### **Deep Tendon Reflexes**

The deep tendon reflexes (DTR's) usually tested include the jaw, pectoral, biceps, triceps, radial and ulnar periosteal, knee, hamstring, ankle, and posterior tibial. Finger and toe stretch responses are similar to deep tendon reflexes. Pathologic reactions include the snout, sucking and grasp "reflexes" and extensor toe movements in response to stimulation of the sole, lateral aspect of the foot or the exertion of downward pressure on the anterior tibial group of muscles and the lower part of the calf muscles. Involuntary leg withdrawal from noxious stimulation and adductor-flexor leg spasms are also pathologic.

In a cerebral or spinal cord lesion, the deep tendon reflexes may vary from total absence to hyperactivity not necessarily depending upon the acuteness or chronicity of the syndrome. A common pattern in a cerebral lesion is a decrease of reflexes in the affected arm and an increase in the ipsilateral leg or vice versa.

To test the DTR's in the arm, sit the patient at the bed or table side and lift the arms with elbows flexed by holding both thumbs with one hand. Tapping the radial border of the wrist results in flexion at the elbow; tapping the ulnar border results in pronation. Placing the arms in the patient's lap at rest, the examiner places his index finger on the biceps tendon and taps it, noting the activity of flexion and/or supination of the forearm. The triceps jerk is tested with patient's palms on his thighs, elbows directed outward, and tapping the triceps tendon near the elbow with the other hand on the triceps muscle to palpate the degree of contraction. An inverted reflex consists of movement not ordinarily associated with the muscle whose tendon is being stretched. Thus, flexion at the elbow when testing the triceps jerk represents an inverted reflex.



In the writer's opinion, this is a central phenomenon determined at the cord level, coupled with nerve root dysfunction at the level which is being tested. Asymmetry and hyperactivity of finger stretch reflexes carry the same connotation as for deep tendon reflexes. The jaw jerks may be tested on a unilateral basis to determine whether asymmetry of response is present. Placing the index finger on the symphysis of the jaws in the midline and striking the finger elicits a summated reflex which cannot be used for lateralizing purposes.

The facial reflex is obtained by placing the index finger on the nasolabial fold, exerting pressure and striking the finger. Facial muscle contraction represents the endpoint and hyperactivity or asymmetry are noted. This also holds true for the palmomental reflex which is obtained by scratching the thenar eminence or the palmar surface of the thumb, noting contraction of the chin or mental muscle on the ipsilateral side.

### **Abnormal Reflexes**

To test for snouting, place a tongue blade or the index finger vertically across the closed mouth and strike it with a hammer. Pursing of the lips in a pouting movement constitutes a positive response and is pathologic. The sucking response is obtained by placing a tongue blade between the lips with eyes closed and noting whether it is grasped by the lips.

To test foot and grasp reflexes the examiner places four fingers, exclusive of thumb, on the palm or sole and draws them forward slowly toward the patient's finger tips, exerting pressure while doing so and increasing the pressure as he approaches the fingertips. If present, the major component of the grasp is flexion of the distal phalanges. The same four fingers drawn forward on the sole of the foot toward the toes exerting pressure upon approaching the metatarsophalangeal joints. A positive response consists of a firm grip on the examiner's finger tips by the toes. Even a moderately positive response will be strong enough to enable the examiner to lift the leg clear of the bed or table.

A convenient method of standardizing the plantar response test is to use a tuning fork with sharp square prongs. One prong is placed on the lateral aspect of the dorsum, the other against the lateral aspect of the sole of the foot and it is brought forward to the small toe. This has the advantage of both standardization and reinforcement. Reinforced stimulation has a greater probability of eliciting an abnormal plantar response than does a single stimulus. The failure of flexion in one foot when the opposite toes show a normal flexor response may be considered to be as significant as a frank extensor response.

By and large, the abdominal cutaneous reflexes are unnecessary in the evaluation of a central lesion above the foramen magnum. Their value increases in cord problems and in certain peripheral problems related to spinal roots. In the latter instance, the reflexes may be divided into three levels, notably D8, D10, and D12. If one of these levels is deficient in producing contraction while the others are active, this may constitute a valuable sign. Each of these segments should be stimulated individually by drawing a sharp instrument across the

abdominal wall, proceeding medially in the horizontal plane, at the infracostal, umbilical, and iliac crest levels.

The examiner should test reflexes repetitively in order to determine whether a particular reflex is readily fatigued out of context with the remainder of the reflexes.

The described methods do not necessarily apply when the patient is in stupor or coma. Nevertheless, certain other techniques may be introduced in such situations.

The weak limbs in a hemiparesis are usually more flaccid than the stronger ones. Flaccidity is generally proportionate to the depth of depression of consciousness. To test for this, the examiner lifts one limb with one hand and drops it onto the other hand, held approximately one or two feet below. If the limb drops as a dead weight, without resilience, it indicates the presence of flaccidity. The legs are flexed at the knees, with the soles resting on the surface of the bed and knees brought into apposition. Then the legs are released. The flaccid leg usually deviates outward. If the flaccidity is not very marked but weakness is present in a leg, the heel may slide forward at a faster rate than the stronger leg, so that the leg resumes the supine position more quickly. If hand and/or foot grasp reflexes are present, unilaterally weaker ones occur on the side of weakness.

Provided that noxious stimuli are perceived, these are useful in determining power during withdrawal from the stimulus. A leg may be tested by repetitively stimulating the sole with a pin with one hand while the other is placed on the knee. It should be remembered, however, that involuntary withdrawal may be stronger than voluntary movement in spinal cord lesions. In the comatose or stuporous patient, it should be observed whether one leg is externally rotated. This suggests weakness. Spontaneous arm and leg activity should be observed. Less movement on one side strongly suggest weakness therein. The lack of spontaneity of movement also applies to the patient who is awake.

### **Patterns of Motor Defect in Cerebral Versus Brainstem or Spinal Cord Disease**

It has been stressed that since weakness due to a central lesion is a defect in movement, other movement deficits will be present. The other deficits are those of dexterity, rapid and fine movements, associated movements, abnormal synkinetic movements, or failure to use a limb spontaneously.

The pattern of movement deficit in cerebral lesions is often similar to that from a brainstem or spinal cord lesion. However, as a rule, brainstem or spinal cord lesions present some evidence of bilaterality, however asymmetrical, if movement deficits are present at all. The anatomic level of the lesion is usually determined by collateral signs. Thus the examiner attempts to find the level, whether brainstem or spinal cord, by determining whether motor disturbance caused by cranial motor nerve or spinal nerve dysfunction is present. This is often impossible in brainstem lesions so that nonmotor signs must be sought. It should be stressed that when motor nerve dysfunction is present the defect is of muscle weakness and not of movement.

### **Patterns of Motor Defect in Spinal Root or Peripheral Nerve Disease**

In weakness from a peripheral lesion the disorder is that of muscle and not of movement. Therefore, unless a muscle or group of muscles is severely affected or happens to be in a functionally strategic position for a given movement there are no associated movement defects.

It is important to attempt a grouping of involved muscles in terms of:

1. The pattern of cranial motor nerve defects
2. The anatomic relationship of the cranial motor nerves to cerebral hemisphere and/or brainstem, and
3. Peripherally, the relationship of involved muscles to a single nerve root, to the brachial or lumbosacral plexus, or to one or more peripheral nerves.

### **Examples of Spinal Root Patterns**

**Cervical Roots.** Weakness of the spinati occurring with weakness of deltoid and biceps suggests a lesion at the level of C5 which is the common denominator root for the muscles described.

Biceps weakness grouped with weakness of the deltoid, triceps, wrist extensors and palmar abduction of the thumb, indicates that the lesion is at C6. There may also be weakness of the latissimus dorsi, serratus magnus and pectoral muscles. Neither the biceps nor triceps jerks need be altered, both may be slightly decreased, or only one of them decreased, but it is apparent that the most prominent denominator nerve root of the muscles involved is C6. A C7 lesion will usually affect all the muscles described under the heading of C6 except the biceps spinati and deltoid, and reflex alteration involves the triceps jerk, and not the biceps. Palmar abduction of the thumb is an important function in both C6 and C7 lesions. In C6 and C7 lesions, some weakness is often detected in abduction of the fingers. However, a secondary thoracic outlet syndrome (anterior scalene syndrome) is a frequent accompaniment of more proximal nerve root lesions. Thus, some evidence of weakness apparently determined by a lesion one or two segments below the highest level may well be due to secondary effect on the brachial plexus.

**Combined Spinal Cord and Nerve Root Lesions.** With combined spinal cord and nerve root syndromes a more or less precise determination of the root level can be made. The nerve root level is absolute and changes only in intensity whereas the spinal cord level of weakness (and sensory changes) is an ascending one, as the lesion exerts a progressive effect. Thus, before the full pattern is in evidence, on day "x" the weakness may be in dorsiflexion of the feet but by day "y" it may have ascended to thigh flexion at the hip.

**Lumbosacral Roots.** Muscle grouping described for the arm applies equally to the leg. In a lesion at L2 or L3, weakness may be detected of iliopsoas action in flexing the thigh on the hip, quadriceps femoris in extending the knee, the adductor group, and the abductor group. The reflex involved in a high percentage of cases is the knee jerk alone. This grouping of muscles also applies to the L4 nerve root. However, since the L4 root also innervates posterior

muscles one may find weakness in the glutei and hamstrings. Likewise, some dorsiflexor toe weakness may be found but it should be stressed that at the L4 level, the L5 nerve root and, in some instances, the S1 will be involved as they pass this level in the spinal canal. In fact, in the usual L4 nerve root syndrome it is very common to find major evidence of involvement at this level and minor evidence of involvement of both the L5 and S1 nerve roots. Atrophy of the buttocks may be noted by having the patient contract the muscles forcibly while the examiner inspects and palpates them.

### **Spinal Root Versus Peripheral Nerve Lesion**

The L5 level presents unique problems in differential anatomic diagnosis. The effect of a lesion at this level most often causes weakness of dorsiflexion of toes and foot. Likewise, weakness of eversion and inversion may be present. Atrophy of the peronei and anterior tibial compartment muscles is an important sign. The differential anatomic diagnosis of a foot drop includes not only an L5 nerve root or peroneal nerve but a central lesion at almost any level from parasagittal cerebral to the spinal cord. To distinguish L5 root and peroneal nerve from a central process other motor signs are sought such as; increase in tone, weakness of plantar flexor movement, increased deep tendon reflexes, gait peculiarity, faulty rapid movements (depending upon the degree of weakness), the presence of better synkinetic than isolated movement in foot dorsiflexion, the plantar response, and the presence or absence of any movement deficit in thigh flexion. As a rule of thumb, atrophy usually indicates that a peripheral problem is present although parietal lobe lesions may be associated with atrophy. To distinguish an L5 root lesion from a peroneal nerve disorder note that the peroneal nerve problem will cause weakness of dorsiflexion and eversion but none in inversion or plantar flexion. Commonly, the peroneal nerve disorder is acute in onset, occurs with weight loss, in knee crossers, and in a setting of alcohol or sedative intake.

### **Peripheral Nerve and Myogenic Lesions**

Peripheral nerve lesions are usually geographically symmetrical but not necessarily symmetrical in degree. The weakness usually starts in the leg distally. Dorsiflexor weakness may be relatively severe while plantar flexion remains strong. Excluding sensory complaints and findings, it is (a) the geographical symmetry, (b) the peripheral location, and (c) the fact that the weakness cannot be linked to a single spinal nerve root that indicate that the lesion is in a peripheral nerve. Sympathetic motor disturbances in the nature of sweat, color, temperature, skin, and hair distribution abnormality are relatively late in appearance. Proximal muscle weakness due to peripheral neuropathy also occurs but when it does, and is purely neurogenic, it is usually abrupt in onset. The writer feels that this is the key factor in distinguishing the purely neurogenic proximal muscle weakness from that which is myogenic. At a stage of moderate weakness reflexes are likely to be preserved in a myogenic process and decreased to absent in a neurogenic one.

In a situation where either a peripheral nerve or a nerve root appears to be the cause of muscle weakness in a single limb, such as the arm, there can be no substitute for a detailed muscle function test. Those muscles responsible for finger movement must be carefully tested. The C8 root is common to both median and ulnar nerve. Therefore, barring anomalous total control by one nerve or the other, weakness of flexion of all distal phalanges (excluding the thumb) would indicate the presence of a C8 lesion whereas weakness only in the radial two fingers suggests a median nerve lesion and weakness present only in the ulnar two fingers indicates an ulnar nerve lesion.

Geographically symmetrical weakness of proximal muscles incorporates the problem of a purely myogenic disorder in the differential diagnosis. As indicated, reflexes are relatively preserved in contrast to a neurogenic condition. All proximal muscles must be carefully tested, however, including extension and flexion of the neck and the testing of pelvic muscles by having the patient attempt to rise quickly from a squatting position. The pattern of gait may also differ with a bilateral circumducted pelvic movement present ("duck waddling") in contrast to the unilateral circumduction seen in a cerebral hemispheric lesion. In all cases of suspected muscle disorder, the muscles are palpated for their consistency. The presence of a muscle disorder does not exclude a concomitant neurogenic one as in hereditary disease, as a secondary effect of cancer, or as an expression of diffuse vascular disease.



# The Examination of Eye Movements

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Examination of eye movements is usually performed in the course of testing the cranial nerves. Eye movements are mediated by the nerves III (oculomotor), IV (trochlear), and VI (abducens). While this is anatomically true, it is important to consider both eyes as a functioning unit which moves together in a conjugate fashion. Normal eye movements are conjugate and influenced by a variety of factors which are not purely "oculomotor." Some of these are vision, vestibular function and general facial motility. Thus, abnormal eye movements may at times reflect primary visual difficulties (blindness or amblyopia), disorders of the labyrinth or of its connections or even a facial palsy. Even though we speak here of examination of the oculomotor function, eye movements should always be considered in the larger context and especially together with vision and with the vestibular functions.

## Neuroanatomical Background

A few basic neuroanatomical facts are essential for the proper understanding of oculomotor dysfunctions. Conjugate movement of both eyes in one lateral direction depends upon impulses descending from the contralateral cerebral hemisphere, *e.g.*, the right side of the cerebrum is primarily responsible for moving both eyes to the left. However, these impulses are influenced by vestibular and probably some other subcortical systems. In a conscious patient, eye deviations are influenced by cerebral and vestibular systems which project upon the brainstem and the cranial nerve nuclei III, IV, VI.

The abducens (VI) nucleus and nerve activate the lateral rectus muscle which when contracted pulls the eye to the ipsilateral side. The trochlear (IV) nucleus innervates the superior oblique muscle of the opposite eye and when primarily activated produces a downward displacement of the eyeball with some degree of rotation—clockwise in the right eye and counterclockwise in the left eye. The trochlear rootlets cross before leaving the brainstem. The trochlear action cannot be seen or tested under the normal circumstances and may become apparent only in cases of oculomotor (III nerve) paralysis. The oculomotor (III) nerve innervates the remaining muscles: the medial rectus which moves the eye primarily in, superior rectus (upward movement), inferior oblique (upward movement with some rotation), and inferior rectus (downward movement). The levator palpebrae lifts the eyelid and is also innervated by the oculomotor nerve. On the other hand eye closure is accomplished by the orbicularis oculi muscle controlled by the fibres of the facial (VII) nerve. Conjugate eye deviation in any direction involves a complex interaction of several muscles, innervated by at least two nerves at any time.

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The oculomotor nerve also participates in controlling the pupillary constriction and dilatation. Sympathetic (dilatation) and parasympathetic (constriction) effects also influence this function.

## The History

Patient's complaints whether spontaneous or elicited provide an important clue to possible eye-movement abnormalities. History of diplopia points usually to some incoordination of movement of the two eyes. This may be due to recent involvement of an ocular muscle or nerve and root. It is usually present only when both eyes are open and will be most pronounced when the patient is looking in the direction which requires contraction of the paralyzed or weak muscle. Monocular diplopia on the other hand is often due to lesions of the visual system (rather than oculomotor) or of the eye media. In some patients further questioning will reveal that their double vision is actually a blurring of vision or oscillopsia (sensation of objects jumping in front of the eyes) in the vertical or horizontal plane. This usually persists even when one eye is covered and is most often secondary to a recently acquired nystagmus and not to a nerve-muscle paralysis. A complaint of "dizziness" can at times be traced to some degree of strabismus.

## The Examination

The actual examination of eye movements may be divided into the following parts:

1. Eye position and movements at rest
2. Eye movements on command
3. Eye movements on pursuit
4. Eye movements upon passive head movements
5. Pupillary reactions
6. Fundus examination
7. Special bedside tests

### Eye Position and Movements at Rest

Looking at the patient one observes the position of the eyes at rest as well as voluntary movements to either side. The position of the eyes relative to the head should be noted (are they in the center or do they tend to deviate to one side more than to the other). The position of the head may indicate an oculomotor dysfunction *e.g.* the head may tilt with brainstem lesion or in patients with some strabismus. The size of the palpebral fissures may hint at some degree of ptosis (III nerve lesions) or levator palpebrae weakness associated with primary muscle disease or pseudoptosis as seen in Horner's syndrome. Greater than usual size of the palpebral fissure may indicate proptosis or lid retraction which provides a clue of brainstem dysfunction or at times facial (VII) weakness on that side. Finally, gross nystagmus on direct forward gaze may be apparent. This is often congenital and of unknown cause but at times may be secondary to brainstem disease. Blinking should be noted. Its paucity will indi-

cate extrapyramidal dysfunction while constant blinking may be associated with ties whose cause is in the great majority of cases undetermined.

### **Eye Movements on Command**

The patient is instructed to perform a series of movements in the order of the examiner's choosing. These are usually "Look straight ahead" followed by "Look to your right," "Look to your left," and then "Look up and down". It is of some importance to get the patient to initiate each movement from the midline and to return to the midline before the next command is given. Normally an individual will have no difficulty in performing any of these tasks but frequently a head movement will accompany the ocular deviation. If this happens, it is still normal for the eye movement to precede the head deviation by a fraction of a second. Further instructions may be given, *e.g.*, "Move your eyes only and not the head". Some normal individuals will complain of discomfort when looking upward and will not be able to sustain upward gaze. The observer will notice whether the eyes move conjugately or whether there is some dissociation between the two eyes or inability to move the eyes in any direction.

### **Pursuit Movements**

These eye movements are essentially the same as movements "on command" but the patient is given an object (usually the examiner's finger) to fixate, which he follows with his eyes. The same sequence is observed as in testing for eye movements on command. Generally speaking, pursuit movements are easier to perform and at times patients who cannot move their eyes well on command will show a normal or near normal eye excursion when given a target to look at. It has been said that this kind of dissociation gives a clue to the location of the lesion—cerebral in cases of defects of voluntary gaze only and "subcortical" in cases when even fixation cannot bring the eyes to a given point. This is generally not true; the defect in pursuit movements indicates simply a greater degree of dysfunction. In many patients one can follow the evolution of this deficit with inability to move the eyes on command appearing first, followed by inability to follow an object, when the disease process progresses, and finally absence of movement on the oculocephalic maneuver (see below). Similarly in patients whose neurologic status is improving (after "strokes" or following radiation of intracranial neoplasms) the reverse sequence may be seen. The oculocephalic reflex returns, followed by pursuit movement, and finally by eye movement on command. The direction of conjugate gaze deficit is an important clinical finding. Paresis of gaze occurs in the direction opposite to the lesion in cerebral and upper midbrain disease. Paresis is ipsilateral in lesion of lower midbrain and pons.

Both the excursion and the quality of pursuit movement are important. The eyes should move all the way to the outer and inner canthi respectively. Some degree of "terminal" nystagmus in extreme deviation is to be expected and is of no clinical significance when the target is in the monocular field (of the abducting eye).

Occasionally the pursuit movements are saccadic or nystagmoid in nature. This may be pathological, *e.g.*, in patients with extrapyramidal disease and an equivalent of cogwheeling. In some individuals an optokinetic effect is created when following an object but this ceases in lateral deviation when the target is stationary. Nystagmus of clinical significance will persist for several seconds after the deviation has been completed. Monocular nystagmus is always significant. It is often associated with a defect in adduction of the other eye as in cases of median longitudinal fasciculus lesion syndromes. Vertical nystagmus (fast component upward or downward) is always of clinical significance.

### **Reaction to Passive Head Movements**

The patient is instructed to look straight ahead or to look at a stationary object while the examiner holds his head from behind. The head is then moved consecutively in all directions. Normally, a passive head movement to the right results in an initial deviation of the eyes to the left (oculo-cephalic reflex), followed by a rather prompt recentering. Subsequently the head is moved to the left (eyes should deviate to the right), down (eyes up), and up (eyes down). Failure of the eyes to move in a given direction usually indicates a rather severe degree of oculomotor dysfunction (gaze paresis) in that direction (V.S.). This test is of particular significance in patients with impaired states of consciousness (see chapter on "The Evaluation of the unconscious patient").

### **Pupillary Reactions**

Normal pupils are round and equal. A very slight degree of diameter asymmetry (1 mm) is sometimes seen and may be congenital or secondary to uneven illumination of the two eyes. Such slight asymmetries should be disregarded. Distortion of the shape of the pupil is often secondary to previous surgery or trauma; this can be easily ascertained. Brainstem disease, especially in the region of midbrain and pretectum is at times associated with abnormal shape of the pupil, *e.g.*, elliptical, oval, or simply irregular pupils.

When a bright light is flashed into one eye, both pupils should contract. This is known as respectively the direct and consensual reflex to light. Failure of the illuminated eye to constrict with preservation of consensual response indicates a defect in the motor mechanism (III nerve) on the side stimulated. Absence of constriction on either side is usually due to a lesion of the optic nerve or retina on the side stimulated (provided no cycloplegic drugs were used prior to the examination).

While testing the pupillary response to light one should pay attention to other factors which may mask a defective response. Thus, if the patient blinks, the pupils will constrict even though there is no response to light. Pupillary constriction is an integral part of the blink response. Ocular convergence and accommodation are also accompanied by constriction. The patient should be ordered to fixate at a distance when the light reflex is tested.

Testing the pupils for reaction to accommodation and in convergence one asks the patient to look at an object several meters away and then to shift his



gaze onto the examiner's finger placed about 20 cm in front of his nose or to look at something he could see at a near point. This maneuver is repeated several times. The pupils should show a distinct dilatation on distant and a constriction on near vision.

The preservation of pupillary constriction on convergence and accommodation and lack of constriction on light stimulation is strongly suggestive of disease of the pretectum as, *e.g.*, with tumors in that area or CNS syphilis. Slow constriction of pupil on attempted convergence or slow constriction in bright illumination or dilatation in darkness is characteristic of a myotonic pupil. This phenomenon forms part of Adie's syndrome, associated with absent deep tendon reflexes, and is of unknown etiology. All patients with an apparent loss of pupillary reaction to light should be placed in a dark room. Normally pupils dilate rapidly in darkness. Similarly, pharmacological agents may be used to determine further the nature of pupillary abnormality. This should never be done in patients with acute intracranial disease since the test may mask abnormal pupillary changes which are of great clinical importance. In a rare patient the apparently nonreactive pupil will constrict after prolonged light stimulation.

### **Fundus Examination**

Inspection of the eye grounds is part of the examination of visual function. Its special significance in the context of eye movements lies in the fact that at times fine oscillations or nystagmoid jerks of the disc may be seen even though on gross inspection of the eyes nystagmus was not apparent. Such oscillations may be easier to see with the patient fixating at a distance. The direction of the fast and slow components will appear reversed because of the negative image seen.

### **Special Tests for Oculomotor Function**

Various simple tests are available to extend the observation of eye movements.

#### ***Forced Eye Closure***

The patient is asked to shut his eyes firmly against resistance. The eyeballs will normally roll upwards and often outwards. The response is usually fleeting and the eyes return to the midline as soon as the active resistance ceases. In some patients with lateralized brain lesions the eyes will often, but not invariably, deviate to the side of hemiplegia even though voluntary movement in that direction may be absent.

In patients with a peripheral facial weakness (*e.g.* Bell's palsy) one eye is often seen to move upward from time to time. This is a normal phenomenon and not a manifestation of dissociated gaze. The inability to close the eye on the weak side renders the normal upward eye rolling upon attempted eye closure very prominent and may be misleading.



### ***Optokinetic nystagmus (OKN)***

This is a normal phenomenon (railroad nystagmus) and easily elicited. The patient is asked to look at a regular tape measure which the examiner moves in front of his eyes from left to right, then right to left, and finally up and down. Other stimuli such as alternating strips of white and black cloth or child's color beads may be used. With tape it is sometimes useful to instruct the patient to read every number aloud. Normal response consists of fairly regular nystagmus with the fast component in the direction from which the tape is approaching. Response should be fairly symmetrical in horizontal and vertical meridians. It is quite prominent in children and young adults and lesser in older age groups. Absence of optokinetic response in one horizontal direction usually correlates with an oculomotor deficit in the same direction and is most likely to be due to a lesion in the pontine or ventral mesencephalic tegmentum of the same side or to a deep cerebral or upper midbrain lesions of the opposite side. Loss of OKN and an homonymous hemianopia are not too well correlated except in cases of lesions deep in the brain.

Loss of OKN in all directions may be due to impaired states of consciousness, inability of the patient to cooperate because of severe mental changes, and also to drug intoxication. Variable degrees of defect in the vertical plane are seen in old age and with brainstem lesions or bilateral cerebral lesions.

### ***Tests for Diplopia and Strabismus***

These are too numerous to consider here but an examination utilizing a red glass and a flashlight will usually be satisfactory to identify the weak ocular muscles responsible for diplopia. The principle rests on identification of the real and false images with the help of the red glass.

In rare patients diplopia will be present only on distant vision and not when the patient is fixating on a near object. This is the syndrome of paralysis of divergence, attributed to a lesion of the central grey matter of the midbrain. No actual muscle weakness can be demonstrated.

### ***Positional Phenomena***

In many patients changes in the position of the head will bring out nystagmus not otherwise apparent or will emphasize and even alter preexisting nystagmus. For details of such testing see chapter on "The Examination of Vestibulo-Oculomotor Function." Positional nystagmus may occur with both posterior fossa and peripheral labyrinthine lesions. Sudden onset of nystagmus, often associated with vertigo, may be observed upon changing the body position from horizontal to vertical and vice versa. Both these effects may be seen in patients with intracranial space occupying lesions (presumably due to mechanical factors such as changes in intracranial pressure and brainstem compression) or with postural hypotension. Nystagmus upon head turning may be also due to interference with circulation in the major neck vessels and secondary transient brainstem ischemia.

### ***Frenzel Lenses***

See chapter on "The Examination of Vestibulo-Oculomotor Function."

***Periodic Phenomena***

In some patients prolonged observation will reveal cyclic changes in eye movements. The eyes may show a forced deviation to the right which shifts to left and back to right every ninety seconds. Prolonged observation may also reveal transient manifestations such as "lightning eye movements," see-saw nystagmus, convergent or retractor nystagmus which may not be apparent at all times. All the above are symptoms of severe brainstem dysfunction. A fortunate observer may at times witness a forced eye deviation which is a part of a convulsive seizure. This will usually localize the responsible lesion to the opposite cerebral hemisphere.

**SUMMARY**

Careful examination of eye movements may provide the examiner with a wealth of clinical information and in many instances will actually localize the lesion. This is especially true of brainstem lesions. But one should again emphasize that eye movements should always be analyzed and interpreted in the proper context of the total neurological picture.

# **The Examination of Vestibulo-Oculomotor Function**

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The clinical vestibulo-oculomotor examination is particularly useful in the diagnosis of disease of the brainstem, cerebellum, or inner ear and in the differential diagnosis of vertigo. It is based on testing the vestibular receptors, the semicircular canals and the saccule and utricle. The semicircular canals will be considered first.

## **Physiology of the Semicircular Canals**

The semicircular canals sense angular acceleration of the head. They are fluid-filled tubes which lie in precise arrangement in each temporal bone. When the head is tipped forward so that the line between the inferior orbital ridge and the external auditory meatus is  $30^\circ$  below the horizontal plane then the lateral semicircular canals are approximately horizontal. In this position side to side head movement or rotation in a turning chair will excite primarily the lateral canals. The anterior and posterior canals are perpendicular to the lateral canals and form angles of  $45^\circ$  and  $135^\circ$  with the midsagittal plane of the head (Fig. 1). Both lateral canals or one anterior canal and the contralateral posterior canal lie in parallel planes on each side of the head.

When the head moves, the fluid in the semicircular canals, the endolymph, tends to remain behind because of its inertia. This endolymph movement bends the cupula and hair cells which project into the canal producing changes in the discharge of the semicircular canal nerves. Movement of the hair cells in one direction increases the firing rate in these nerves while movement in the opposite direction decreases it. During angular acceleration the fluid in both canals in the same plane on the opposite sides of the head reacts simultaneously but oppositely. Both canals act synergistically to produce compensatory eye and postural movements which help maintain equilibrium and the gaze angle in space. Activation of a single canal is sufficient, however, to induce active eye movements. Eye movements from the individual semicircular canals in the monkey are shown in Figure 2. These are similar to those which would occur in humans.

## **Technique of Caloric Testing**

Clinically the most convenient test of semicircular canal function is the caloric test. By application of heat or cold to the canal wall convection currents are induced. These currents produce deflection of the cupula and hair cells and are associated with active eye and postural movements, a sensation of vertigo, and autonomic activation which may include nausea, vomiting, tachycardia and sweating.

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Lateral canal function is usually tested during the caloric examination. For this the head is tipped back so that the line between the infraorbital ridge and the external auditory meatus is  $60^\circ$  above the horizontal plane (Fig. 3). Then

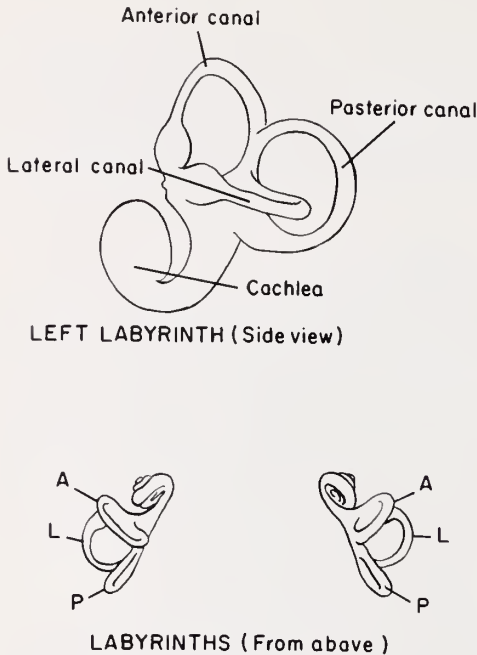
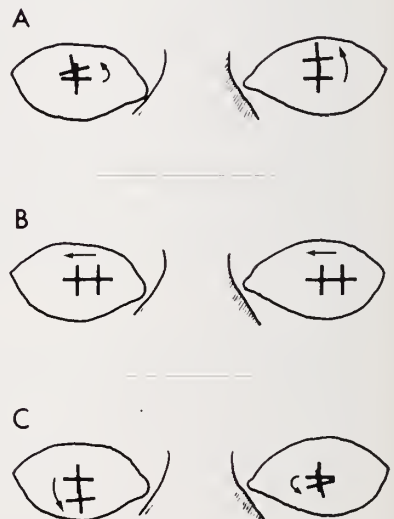


FIG. 1. Diagrammatic representation of the labyrinth, side view (upper) and top view (lower). Each of the canals is parallel or perpendicular to the others and both lateral canals or one anterior and the contralateral posterior canal lie in parallel planes. The enlargement in each semicircular canal is the ampulla and houses the receptor. The saccule and utricle lie in the central vestibule connecting the three canals and the cochlea is anterior to them.

FIG. 2. Eye movements induced in the monkey by electric stimulation of the left anterior canal (A), left lateral canal (B), and left posterior (C) canal nerves. These movements are similar to those which would occur in man. The first cross shows the position of the eyes at the beginning of stimulation and the second cross the eyes at the end of stimulation. The arrows indicate the direction of movement. When the lateral canal is electrically stimulated the eyes move horizontally in the same plane as during nystagmus induced by hot or cold caloric stimulation with the head back.



the lateral canal is vertical and heat or cold are most effective in producing movement of the endolymph. Cooling may be induced in several ways: Several drops of alcohol may be instilled into the external auditory canal and evaporated

with a jet of air. More often water below the body temperature is used. Ten cc of water at room temperature are delivered over a ten second period and the induced eye movements, sensation, and body postural changes are observed. If the caloric response is markedly depressed or absent then a continuous flow of ice water for three minutes will help determine whether any lateral canal function is present. Heating is usually produced by douching the external auditory canal with water above the body temperature, commonly at  $44^{\circ}\text{C}$ . The external

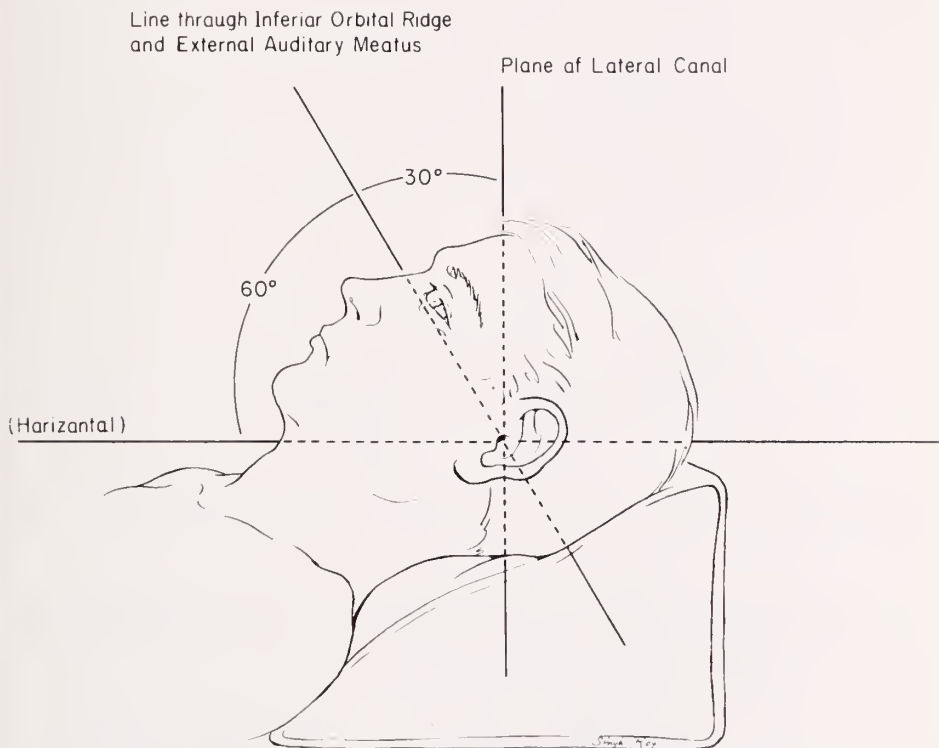


FIG. 3. The position of the head during caloric testing which maximizes the lateral canal response. The head is placed so that the line between the external auditory meatus and the inferior orbital ridge is approximately  $30^{\circ}$  from the vertical. Then the lateral canal is approximately vertical and hot or cold water introduced against the drum is most effective in producing horizontal nystagmus.

canals should be free of cerumen during caloric testing and the drums should be examined first for the presence or absence of perforation. Cooled or heated sterile saline may be used if the drum is perforated.

Soon after hot or cold water is injected into the external ear, active jerky nystagmus is induced. The eyes move slowly toward one side and quickly toward the other. By general agreement the direction of nystagmus is usually indicated by the direction of the quick phase. Nystagmus induced by caloric stimulation is observed for direction and vigorousness of response. The presence or absence of vertiginous sensation should be noted and past-pointing can be determined. With cold caloric stimulation the direction of the quick phase of



the induced nystagmus is contralateral and with hot calories it is ipsilateral to the stimulated side. Vertical nystagmus can be induced by bilateral simultaneous hot or cold caloric stimuli with the head upright. With hot calories the quick phase of the nystagmus is up and with cold calories it is down.

### Interpretation of Results of Caloric Tests

If the reaction to both hot and cold caloric stimuli is decreased in one ear, then the pathologic process probably involves the peripheral labyrinth or the eighth cranial nerve on that side. In contrast, if nystagmus in one direction is depressed, *i.e.*, if nystagmus induced by cold caloric stimulation of one ear and hot of the other is less active than the converse, there may be a central lesion. If the lesion is central it is ipsilateral if below the oculomotor decussation and contralateral if above it. The oculomotor decussation is at the level of the third nerve nucleus. Electric stimulation above the decussation causes the eyes to move contralaterally and lesions produce paresis of contralateral gaze.

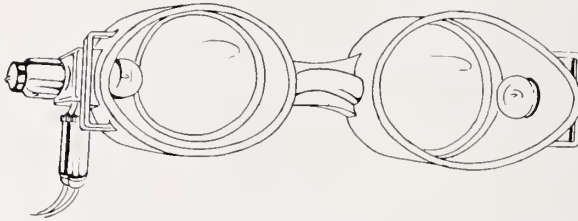


FIG. 4. Frenzel glasses, seen from the patient's point of view. High diopter lenses prevent fixation and the bulbs permit observation of the eyes while the patient is wearing the glasses.

Below the decussation the effects of stimulation and lesions are ipsilateral. For details of the central oculomotor system see Chapters 2-4 in *The Oculomotor System*, P. B. Hoerber, 1964.

Mixtures of central and peripheral disease are not uncommon particularly with neoplasms in the region of the eighth nerve. In this case the caloric response will frequently be absent on the affected side and a characteristic type of gaze nystagmus is present. When the patient looks toward the side of the lesion, the nystagmus is coarse while on gaze to the opposite side fine beats of nystagmus are observed. This type of nystagmus is most commonly seen with tumors of the eighth nerve (acoustic neurinomas) and is not produced by peripheral disease alone.

### Frenzel Glasses

It is a frequent finding that spontaneous gaze nystagmus or nystagmus induced by vestibular testing may be markedly suppressed or absent during visual fixation but may be striking when fixation is abolished. Thus observation of eye movements is greatly aided by the use of Frenzel spectacles (Fig. 4). These have high positive lenses of twenty diopters with a small light at each external canthus. They may be readily obtained commercially. When

they are in place the patient's eyes appear magnified to the observer while the patient cannot clearly see objects more than a few inches away. With Frenzel spectacles weaker caloric stimuli (*i.e.*, water closer to body temperature) can be used which produce only a weak sensation of vertigo and little or no nausea.

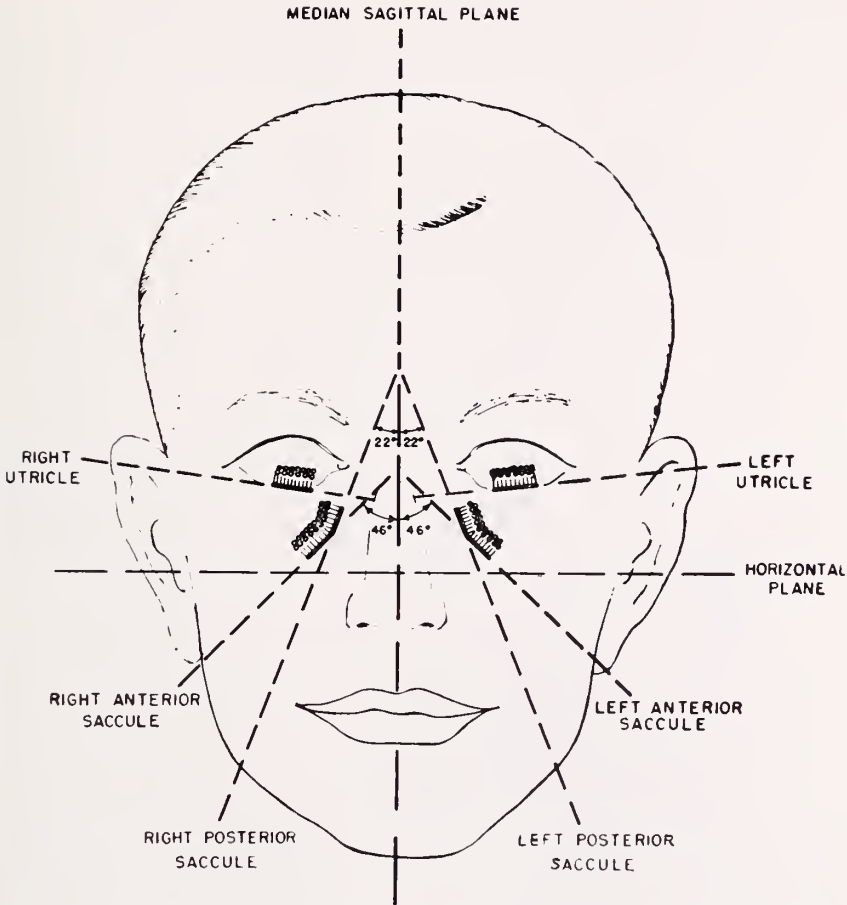


FIG. 5. Diagram of the orientation of the utricular and saccular maculae. Reprinted with permission from E. F. Miller II, *Acta Otolaryngologica* 54: 479-501, 1962.

Frenzel spectacles are particularly valuable in examining for the presence of nystagmus during head position or positioning tests.

### Physiology of the Utricle and Saccule

The otolith organs, the utricle and the saccule, which sense static head position and linear acceleration of the head, are horizontally and vertically oriented, respectively (Fig. 5). (There is controversy about the function of the saccules but evidence points to their involvement in positional and positioning responses. For the purposes of this discussion they will be considered together

with the utricles.) The otolith receptors are composed of hair cells which have crystals of calcium carbonate fixed to their tips. The calcium carbonate crystals react to gravity or linear acceleration and bend the macular hair cells. This changes the resting discharge in the utricular or saccular nerves. Tilting the head toward one side induces an increase in the resting discharge in the utricular nerve on that side and a decrease in the discharge of the nerve on the opposite side. When the utricles or saccules are stimulated by a static head

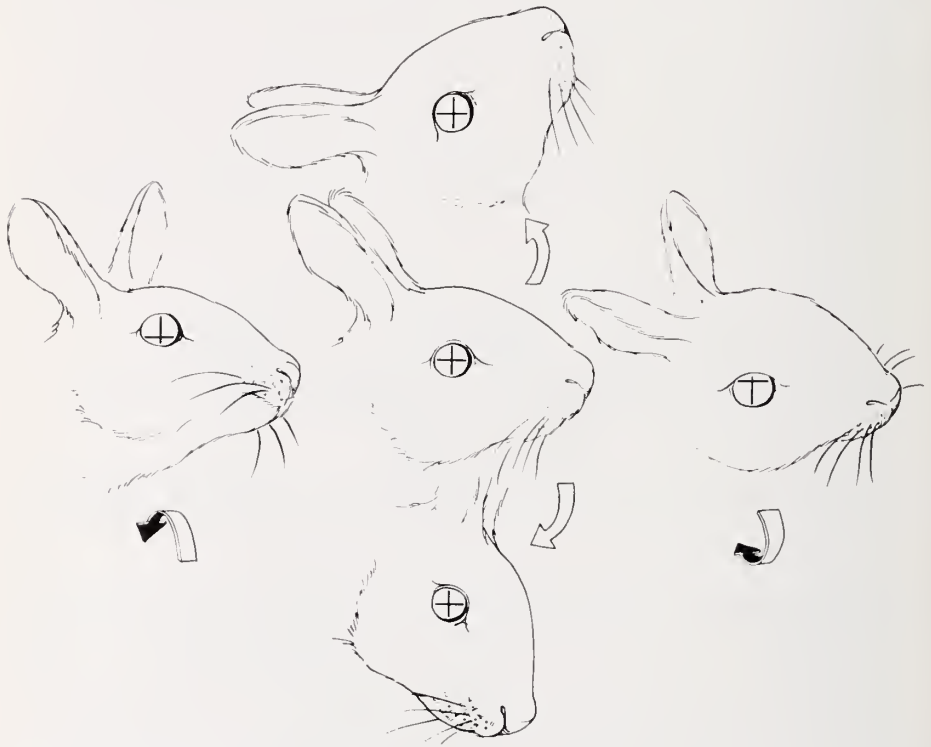


FIG. 6. Diagrammatic representation of the counter-rolling eye movements induced by head position changes, in the rabbit. The cross is fixed to the cornea and shows that the position of the eye tends to remain stationary in space despite changes in the position of the head. When the snout is raised the eyes roll forward and when it is lowered, they roll back. Tipping the head to the left causes the left eye to roll up and the right eye to roll down. The converse is seen when the head is tipped to the right.

position or by the act of head positioning, compensatory or counter-rolling eye movements are produced. For example, when the head is tipped to the left, the eyes tend to move to the right and when the head is tipped forward the eyes tend to roll up. These movements are particularly strong in the rabbit (Fig. 6). Counter-rolling is weak or nystagmus may be induced if the utricle or its nerve on the lowered side is diseased.

### Technique of Testing the Otolith Organs

Since positional and positioning eye movements are most effectively seen when fixation is abolished, testing is usually performed with Frenzel spectacles. After

observation for spontaneous nystagmus on direct forward gaze the patient's head is slowly moved into various positions. The eyes are observed with the head tipped to the right, to the left, backward, and forward. Adequate time is

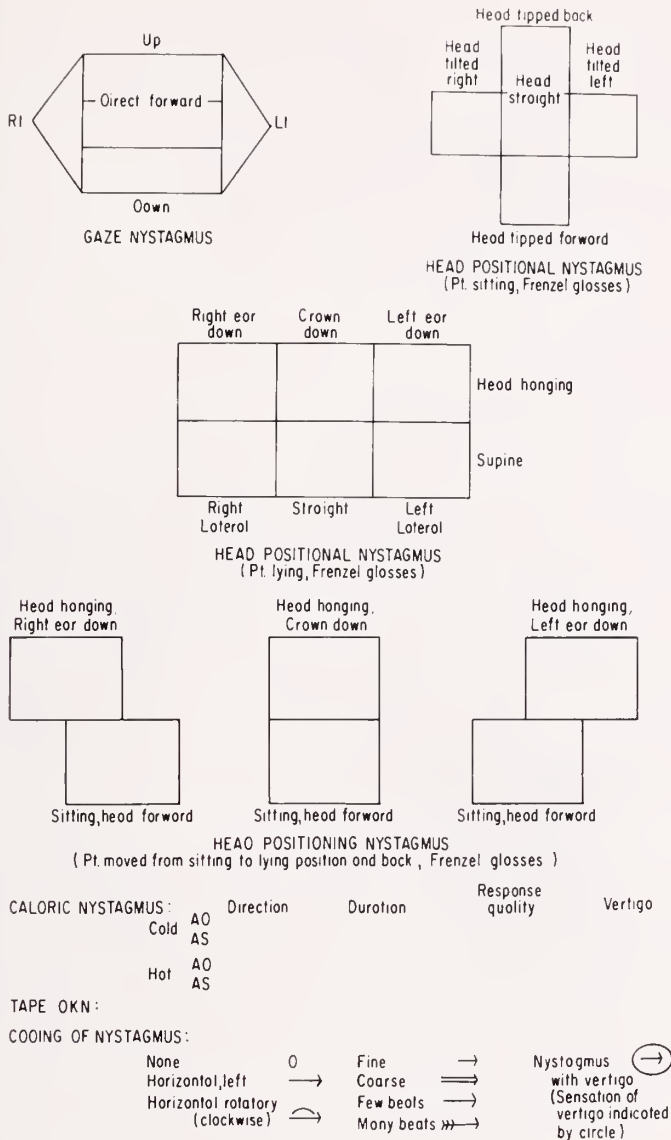


FIG. 7

allowed in each position for nystagmus to develop (from 30 seconds to one minute). The direction and appearance of nystagmus and the presence of vertigo is recorded (Fig. 7). The patient is then moved into the right lateral, left lateral, and supine positions, followed by the head hanging positions with the right ear, crown, and left ear down (Fig. 8).

Positioning tests are performed by moving the patient in a firm but rapid fashion from a sitting position with the head tipped forward to a supine position with the head hanging back. The head hanging positions are particularly valuable for eliciting nystagmus and vertigo. Frequently nystagmus will be induced and a patient's complaints of vertigo verified only when the head is down. The patient should be tested several times in each of the head hanging positions, that is, with the left ear down, the right ear down, and the head straight back with the crown down.

### Interpretation of Positional and Positioning Tests

There is still controversy about the interpretation of the results of head position and positioning tests. In general, however, when horizontal rotatory



HEAD HANGING POSITION  
CROWN DOWN

FIG. 8. Head hanging position, valuable in testing for presence of positional or positioning nystagmus. The head is straight back with the crown down. Two other head hanging positions are of value: head hanging with the left ear down, and head hanging with the right ear down.

nystagmus is elicited in only one position, *e.g.*, with one side down, when the direction of the nystagmus does not change in other head positions, and when vertical nystagmus is absent, then it is likely that peripheral disease of one labyrinth or eighth nerve is present. Usually the disease is on the side which produced nystagmus when depressed. On the other hand, vertical nystagmus and direction-changing nystagmus suggest central disease. Direction-changing nystagmus is nystagmus which is in one direction with the head tipped to one side and in the other direction with the head tipped to the opposite side. Findings from each part of the examination as well as from the general neurological examination are correlated. Diagnosis is made from a pattern of dysfunction, not from a single finding.

Differentiation of disease of the labyrinth or eighth nerve from disease of the central oculomotor system is also aided by examination of optokinetic nystagmus. This is tested simply at the bedside by the use of an ordinary



tape measure. For details of this technique and interpretation of results see "The Examination of Eye Movements."

### **Postural Tests**

Postural responses during caloric testing may also be of some value in localizing the side of disease process. These may be elicited by tandem walking, past-pointing, walking with eyes closed, or the stepping test. In the stepping test the patient marches in place with his hands outstretched and his eyes closed. Normal individuals will not veer significantly to either side while patients with disease of one labyrinth or the brainstem on that side will usually stagger or move toward the diseased side. Postural testing is also of value in diagnosing disease of the otolith organs. The patient is placed on a tilting board with eyes open and closed and tilted to either side. Postural compensation will be significantly less when he is tilted with the diseased side down.

### **Electronystagmography**

In this brief description quantitative testing has not been mentioned. Duration of the caloric response and the number of beats during ten seconds of the most vigorous response are two of the simplest parameters to measure. Electronystagmography also greatly increases the power of the examination and should be used wherever possible. This involves electrical recording of the eye movements induced by vestibular and optokinetic stimulation. Measurements are then easily made of eye velocity during the slow and fast phases of induced and spontaneous nystagmus and of the frequency and amplitude of nystagmic beats. Excellent reviews on electronystagmography and eye movement disorders are to be found in the *Acta Otolaryngologica*, Supplements 129, 1956; 137, 1958; 189, 1964, and in Chapter 19 of *The Oculomotor System*, P. B. Hoerber, 1964.

# **The Evaluation of the Unconscious Patient**

## **INCLUDING OCULO-CEPHALIC AND VESTIBULO-OCULAR TESTING**

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### **PART I. GENERAL AND NEUROLOGIC EXAMINATION**

#### **The History**

In evaluating the unconscious patient the physician is at a disadvantage inasmuch as he cannot obtain valuable information ordinarily available from the mental and sensory examinations. Of course, he must obtain a careful history, for this is by far the most important part of any neurological examination, particularly so with the unconscious patient. Unfortunately, in many instances when a patient is admitted to the emergency room the history is not available. When relatives or other informants can relate the story which led to the episode of loss of consciousness they should be asked whether the patient: 1) used drugs (alcohol, narcotics, tranquilizers, anticoagulants), 2) had a mental illness (difficulty in sleeping, crying spells, feelings of depression or agitation, suicidal ideas or attempts, previous hospitalizations for mental illness, psychiatric treatment), 3) had an injury, particularly to the head, recently or in the past, 4) had seizures or other types of loss of consciousness ("fainting spells," "blackouts"), 5) had a history of previous medical and neurologic illnesses (heart disease, hypertension, kidney disease, diabetes, allergies, previous "strokes") or 6) was exposed to occupational hazards such as fumes, sprays or chemicals. In addition to the medical, a detailed social history should be obtained. As a rule, it is difficult to obtain a complete history when the relatives or friends are concerned about the patient's state of consciousness but, nonetheless, attempts should be made to obtain as many facts as possible.

In general almost forty per cent of the patients admitted for altered states of consciousness have excessive alcoholic or drug intake. The most common drug is barbiturate. Other drugs such as anticoagulants may produce loss of consciousness indirectly as a result of intracranial (cerebral or subdural) bleeding. Insulin and other hypoglycemic drugs have been responsible for a significant number of unconscious states in people whose diabetic condition is not controlled properly through neglect or intercurrent illnesses.

In patients admitted with obvious injury to the head, one should not readily assume that this is the cause of the unconscious state since the head injury may be only secondary to vertigo, syncope, or seizures, and therefore information as to the patient's state of health just prior to the loss of consciousness is essential.

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## Inspection and General Examination

Careful inspection of the patient and his belongings may give significant clues as to etiology. An obvious physical sign should not divert the examiner from making an overall inspection. A search of the patient's clothes may uncover a card stating that he has diabetes or epilepsy. At times, appointment cards for medical clinics may be found among the patient's belongings. At other times empty or partially empty bottles may contain drugs. The condition of the patient's clothes may suggest a struggle or assault. All clothes should be removed and a careful inspection of the patient's head, limbs, and trunk should be made. Lacerations, ecchymotic areas and abrasions should be noted. The scalp should be palpated carefully. At times the only clue that the patient received a head injury may be a greenish-yellow discoloration in the mastoid region commonly associated with a fracture at the base of the skull. Careful examination of the mouth, throat, nose and ears should be made for evidence of blood or infection. The color of the skin and conjunctiva should be noted. Carbon monoxide poisoning frequently produces a cherry-red appearance to the lips. Jaundiced skin and conjunctiva may be the reflection of liver disease with a bleeding tendency. Severe dryness and pallor of the skin with evidence of a loss of scalp hair may suggest hypopituitarism. Multiple ecchymotic areas should make one think of a blood dyscrasia as well as trauma. Petechiae may be seen with infection and blood dyscrasias. Cyanosis may be related to laryngospasm or other mechanical factors involving the respiratory system. The skin should also be examined carefully for the injection marks characteristic of narcotics addicts and diabetics. Odor of the breath may give clues as to alcohol, uremia, and diabetic acidosis. The character and rate of respirations should be noted along with pulse and heart sounds.

The abdomen should be examined as to distention, rigidity, and response to palpation. Not infrequently a mass is palpable, or an apparently large liver and spleen are detected that may be significant as to etiology. The overall attitude of the body should be noted. This includes the relationship of the limbs and head to the trunk. The position of rigid extension of the limbs and retraction of the head may be seen with severe infections of the nervous system and with subarachnoid hemorrhage. Many cases of subarachnoid bleeding do not have meningeal signs in the first twenty-four to forty-eight hours.

## Neurologic Examination

While it might seem that in the unconscious patient a complete or adequate neurologic examination is not possible, careful observation of the response to usual neurologic tests and the employment of special bedside tests frequently reveal significant information.

The following information is based on the experience of the neurology staff of The Mount Sinai Hospital over a fifteen-year period. Observations were made on (A) Patients without neurologic disorders who were rendered unconscious by intravenous barbiturates, anesthetic agents, electro-convulsive

treatment, and patients admitted in coma as a result of drug overdose, or cerebral anoxia; (*B*) patients admitted in coma from other causes, *e.g.*, occlusion of major vessels to brain, intracranial cerebral and subarachnoid hemorrhage, trauma, infections, neoplasia and postictal states.

### **Funduscope Examination**

**Group A.** In group A we were not able to detect significant change with respect to the optic discs, the vessels, or the color of the retina; the fundi were examined in only about twenty-five per cent of the patients. In drug intoxication during stupor or recovery stage of coma one may observe retinal nystagmus.

**Group B.** In group B the funduscope examination proved to be of great value as to etiology but of no value in determining the state of unconsciousness. It is obvious that such findings as papilledema, with or without hemorrhages, and retinal hemorrhages and exudates indicate that one is dealing with pathology such as mass hemorrhage, infection, or malignant hypertension among others. Occasionally certain drugs such as quinine will produce spasm and blanching of the arteries. We have seen a patient where one retina revealed a blurred optic disc with several hemorrhages, and following recovery from coma, visual field testing showed a large central scotoma indicating an optic neuritis rather than papilledema. Gross retinal and pre-retinal hemorrhages have been seen in two cases of lead poisoning.

### **Pupils**

**Group A.** In general, the pupillary light reflex was lost only in the deepest stages of unconsciousness. This was noted primarily in patients with barbiturate poisoning without previous history or other evidence of neurologic disease and in patients undergoing general anesthesia (comparable to second plane, third stage) for elective surgery. In all the cases where deep barbiturate sleep was induced the pupils still constricted to light. In all patients, except in three instances, no significant pupillary inequality was observed. In the three cases where it was observed, there was a history of previous trauma to that eye, although we were not completely satisfied with this explanation. Hippus was observed in approximately twenty per cent of the cases in early stages of induced unconsciousness. In no case of this group was there unilateral pupillary fixation to light. In cases of Doriden or similar drug poisoning the pupils may be dilated. In cases of shock where Aramine or other adrenaline substances are used to maintain blood pressure the pupils may be dilated. In cases of anoxia the pupils may be dilated and fixed. Of course, in late stages of intoxication just before death pupils are most often dilated and fixed.

**Group B.** The failure of both pupils to constrict to light was frequently found in the deepest stages of unconsciousness. However, where there was bilateral absence of pupillary response to light associated with other signs indicating that the patient was in a relatively light stage of unconsciousness, brain-

stem pathology was suspected and confirmed in two cases that subsequently came to autopsy. In six other cases additional ocular signs pointing to brainstem involvement were also present. A unilaterally fixed pupil associated with outward deviation of the eye, with or without ptosis of the eyelid, usually indicated third nerve damage. This resulted from either peripheral or brainstem pathology, frequently secondary to a supratentorial lesion. In four instances this represented third nerve compression by an aneurysm. A unilateral dilated pupil not responding to light did not always indicate the side of the lesion. In three cases of proved subdural hematoma, the hematoma was found on the side opposite to the dilated, fixed pupil. Bilaterally fixed pupils in an unconscious patient may represent blindness from an already existing pituitary tumor or a pre-existing luetic infection. A frequent finding in relation to pupillary size was the fluctuating and alternating inequality of the pupils over time. This has been responsible for much anxiety to those with relatively little experience with unconscious patients because of the fear of a developing epidural hematoma. In our experience, one pupil must become progressively *fully* dilated and *fixed* to be of significance in terms of subsequent management. Small pupils (pin point) with or without excursions to light, may be seen with codeine or morphine poisoning or occasionally transiently with brainstem pathology. Dilated, fixed pupils may be found in cerebral and brainstem trauma, or in late stages of intracerebral or subarachnoid bleeding.

### **Eyelid Tone and Closure**

**Group A.** Eyelid tone is tested by passively raising the lid and observing its fall back into place. The lid reflex can be elicited by quickly flicking the eyelash. In all the cases of unconsciousness induced by drugs or anesthetic agents, when the patient no longer responded to auditory stimuli nor could be aroused by painful cutaneous stimuli, the eyelids began to take on a doughy tone so that when the lids were passively raised they would fall back very slowly. This seemed to coincide with the loss of the eyelash flicker reflex. In deeper stages of induced sleep or in patients with barbiturate poisoning or deep stages of anesthesia, the doughy tone of the eyelids was very apparent, and in many cases, by raising the eyelids passively the eyelids would stay open at least partially. This may be significant insofar as so-called "coma vigil" is concerned, where the patient in a comatose state seems to be looking at a point in his environment. Also, one lid can be passively closed and remain partially closed and the other lid passively made to stay partially open. This would give the impression of a unilateral ptosis. Early in induced unconsciousness, resistance to passive eye opening was observed in over fifty percent of the cases. This resistance to passive eyelid opening is often thought of as indicating a psychogenic disorder. We found that not to be a very reliable sign.

**Group B.** The doughy eyelid with little tone associated with an absent eyelash flicker reflex was commonly observed in the deeper states of coma. Unilateral eyelids ptosis was only considered to be true ptosis if there was a dif-



ference in tone and behavior from the other eyelid. This was seen in patients with aneurysm and associated third nerve involvement and could be detected readily in the early stages of unconsciousness. However, in the deep stages of unconsciousness no definite statement could be made from the reaction of the eyelids alone. The patient in coma with eyes open and seemingly looking at the environment is frequently referred to as being in "coma vigil." As was mentioned before, in many patients in deep coma the eyelids may be passively opened or closed. "Coma vigil" is simply a descriptive entity and in our opinion does not have anatomic or etiologic significance. We encountered four patients considered to be in "coma vigil" since the eyes were open and there were no movements of the face and limbs and absent corneal reflexes. However, when the patients were asked: "If you hear me close your eyes," there was an immediate and definite response of eye closure revealing that the patient was not unconscious but suffered from a severe brainstem lesion with paralysis from the face down. Subsequently, contact could be made with the patient by arranging a "yes and no" system related to eye closure. Although they are relatively rare occurrences, every time that it is vaguely possible that the patient may still be in contact, such questioning should be carried out. In some cases the eyes are open and there is spontaneous movement of the eyelids but the patient is otherwise motionless (except for reflex movement of a limb) and mute. This syndrome is usually found in diffuse brain dysfunction.

### **Ocular Position and Ocular Movements**

**Group A.** Early in induced unconscious states, we found no definite pattern as to the position of the eyes. The instant that the eyelids were passively opened, the eyes were in the position of partial upward gaze and slightly diverted but immediately dropped to the mid-position and began wandering from side to side with or without slight dysconjugation. With barbiturate induced unconsciousness, horizontal nystagmus is frequently observed. This nystagmus can be elicited consistently prior to the patient's lapse into sleep. As the unconscious state is deepened with the administration of more barbiturates, less and less wandering or roving movements are noted. The eyes gradually begin to fall into or near the mid-position so that in most cases of barbiturate poisoning or in deep anesthesia, the eyes are found in the mid-position with slight divergence. Whether the eyes are fixed in the mid-position at this stage can best be determined by the oculocephalic reflex and caloric stimulation. In one instance, a pre-existing phoria resulted in one eye's remaining deviated upward and outward. This was noted prior to the barbiturates and became more apparent during administration of the drug.

**Group B.** The eyes of the patients in the deepest stages of coma, no matter what the etiology, were found to be in or near the mid-position with slight divergence. In one instance, a patient followed for thirty days in such a state showed a change from the mid-position to downward gaze several days prior to expiration. This patient had a basilar artery occlusion proved on post mortem examination. In other stages of unconsciousness the eyes may be in skew

deviation, tonic deviation to one side or the other, or at times tonic deviation of one eye and at other times the other eye suggesting the syndrome of the median longitudinal fasciculus. Tonic deviation of the eyes to one side as the only sign is difficult to evaluate. It is seen commonly following a one sided convulsion on the side opposite the deviation and may indicate a large unilateral cerebral lesion. Tonic deviation of the eyes may represent a subclinical seizure in progress. Deviations of the eyes in the vertical plane may represent bilateral brainstem involvement. The best methods of eliciting ocular movements in the unconscious individual are the oculocephalic maneuver and caloric stimulation.

### **Corneal Reflex**

**Group A.** The corneal reflex was quite unreliable as a measurement of unconscious states since this reflex was absent in early stages of unconsciousness in about forty per cent of the patients and varied as to the time of its disappearance in the remainder. In addition, it is well known that in cases of hysteria or catatonia this reflex may be absent. In subjects under hypnosis, the corneal reflex was eliminated very readily by suggestion. In the deepest stages of unconsciousness, the corneal reflex disappeared along with many of the other reflexes. Unequal corneal responses were found in about ten per cent of the cases for which we had no adequate explanation.

**Group B.** Here again, the corneal reflex showed no consistent pattern and gave no predictability as to depth or stage of unconsciousness since it often disappeared early. Unilaterally absent corneal response may be of lateralizing significance in early phases of unconsciousness and is occasionally seen with associated hemiplegia on the same side.

### **Noxious Stimuli**

**Group A.** The simultaneous stimulation with noxious stimuli (pin prick) of homologous parts of the body, usually the soles of both feet and palms of both hands, is one of the most helpful methods of comparing the behavior of one side to the other. It is one of the most effective ways of eliciting a unilateral defect, whether motor or sensory, in the unconscious patient. In Group A double simultaneous pin prick stimulation of the feet and hands elicited approximately equal withdrawal in all cases. In the deepest states of unconsciousness as in barbiturate poisoning and deep anesthesia, seventy per cent no longer responded with any movements and the remaining thirty per cent showed slight reflex withdrawal of one or both limbs. Other types of noxious stimuli such as supra-orbital pressure, pressure exerted between both jaws, strong pressure on the sternum, loud noises and pungent odors were also utilized. It was found that with a loud noise stimulus the response would disappear relatively early in induced unconscious states. Pungent odors and other olfactory stimuli, such as amyl nitrite and ammonia, produced a withdrawal response up until rather late in unconsciousness in the few patients so tested. Supra-orbital, jaw, and sternal pressure varied in producing responses. For the most part, some sort of withdrawal movement or facial grimace persisted until deep sleep in the

cases of induced barbiturate unconsciousness and was found to be absent in ninety per cent of the barbiturate poisonings and patients under general anesthesia. Noxious stimuli did not elicit decerebrate phenomena in any of the cases of the group.

**Group B.** The method of double simultaneous noxious stimulation proved very fruitful in eliciting laterality in almost all of the cases subsequently shown to have unilateral cerebral lesion or a discrete brainstem lesion. In one case, double simultaneous stimulation of the face elicited movement of the right side of the face only. Double simultaneous stimulation of the limbs elicited movements only of the left limbs. This indicated a crossed brainstem syndrome; left face and right extremities, and was corroborated by post mortem examination. The consistent failure of the limbs of one side to move, or one side of the face, indicates either a sensory or a motor deficit.

Other noxious stimuli such as supra-orbital, jaw and sternal pressure also elicited movement on one side of the body and decerebrate phenomena. We have seen decerebrate phenomena of one side; for example, extension and internal rotation of one upper limb. However, we were not able to correlate any special localizing or lateralizing significance in this particular case.

### Deep Tendon Reflexes

**Group A.** The deep tendon reflexes were unreliable indicators of unconscious states. The disappearance of the deep tendon reflexes occurred in only ten per cent of the patients in the deepest state of unconsciousness of this group. In over sixty per cent, however, they became depressed at this stage. The two patients under hypnosis were unable to suppress the reflexes no matter how great the suggestion.

**Group B.** The presence or absence of the deep tendon reflexes gave little information as to the stage of unconsciousness except that in the very deepest stages they were commonly absent. It should be noted that there were cases just prior to death that still had deep tendon reflexes. Two patients that remained in deep coma for as long as thirty days failed to show disappearance of the deep tendon reflexes although they did become depressed. Absent or markedly depressed deep tendon reflexes may have antedated the comatose state, particularly in diabetics. Marked hyperactivity of deep tendon reflexes on one side may indicate contralateral cerebral pathology.

### Pathologic Reflexes

**Group A.** The only pathologic reflex that was tested was the plantar response. In six patients, transient, unilateral, or bilateral Babinski signs were obtained during the early stages of unconsciousness. We could account for no special reason for this occurrence but it may be significant to note Savitsky and Madonick's finding that approximately four per cent of the average population was found to have the Babinski sign.

**Group B.** Bilateral Babinski signs were not uncommon in the cases of meningeal irritation (hemorrhage, infection), cerebral, and brainstem disorders. It was also not uncommon in the same patient to observe Babinski signs that were present at one moment and absent at another. Persistent unilateral Babinski signs occasionally accompanied other signs referable to that side, or if not, was only significant as an indicator of central nervous system pathology. Abnormal plantar responses did not give any clue as to the stage of unconsciousness, although on a few occasions a previously existent Babinski sign was no longer elicited prior to expiration.

### Meningeal Signs

**Group A.** With few exceptions no meningeal signs could be elicited during the entire course of induced unconsciousness. Resistance to passive flexion of the head was noted in three patients relatively early in the course of induced unconsciousness. We have no explanation for these findings. In one of the cases it was associated with transient generalized rigidity.

**Group B.** Meningeal signs were present in approximately seventy per cent of the patients on the initial examination of cases proved to have subarachnoid bleeding or infection. The remainder had no evidence of meningeal signs on initial examination. On occasion, frank meningeal signs disappeared with the rapid deepening of unconsciousness. At times, resistance to passive flexion of the head was associated with generalized rigidity. Two cases of head injury were interpreted as having meningeal irritation by virtue of resistance to passive flexion of the head associated with facial grimacing as if in pain. Both cases had clear spinal fluid and were subsequently shown to have associated fractures of the cervical vertebrae. It should be emphasized that the *absence* of meningeal signs does not preclude meningeal pathology. A significant number of patients with subarachnoid hemorrhage or infection did *not* have meningeal signs until 24 to 48 hours after admission.

### Motor Phenomena

**Group A.** Motor power may be evaluated by having the patient raise his arms and observe if there is a tendency for one upper limb to drift or fall significantly more rapidly than the other just prior to induced sleep by intravenous barbiturate while the patient is lethargic, yawning, euphoric, and showing a nystagmus, or by raising the lower limbs flexed at the knees and feet on bed and noting any difference in return to the resting, reclining position. In deeper states, the rate and character of fall are different than in the lighter stages. At least twenty of the patients in this group showed a difference from side to side but only in two was this difference consistently on one side. Here, too, we were unable to account for this consistent difference by anything in the history or any other parts of the examination. Not infrequently, the administration of intravenous barbiturates produced, at the stage of deep sleep, transient twitching of the fingers of one or both hands. We have not seen this



with other drugs and have no idea as to why it occurs so commonly with barbiturates.

**Group B.** Focal or one sided seizures correlated well with the expected side of pathology although in two instances the lateralized seizures were opposite the side of the major pathology as proved by post mortem examination. Occasionally, what is interpreted as a generalized seizure represents decerebrate phenomena and this carries with it a difference in interpretation from that of the true convulsion. The reverse may occur, and in one of our cases it was reported that the patient had "decerebrate seizures," and because of the findings of four limb weakness and bilateral Babinskis, was thought to have a brainstem lesion. This case subsequently was proved to be bilateral cerebral disease secondary to bilateral internal carotid artery occlusion. One should observe carefully for any other abnormal involuntary movements. Hemiballismus is occasionally seen associated with unconsciousness. Generalized tremors, twitchings or "flapping movements" may be seen in toxic-metabolic disorders such as uremia and hepatic failure. The motor phenomena per se do not give very helpful clues as to the stage of unconsciousness. Restless involuntary movements do not necessarily mean that the patient is in a light stage of unconsciousness. Although generally it is true that sleep and unconscious states cause the disappearance of most pre-existing abnormal involuntary movements, we have seen certain involuntary movements persist in the deepest stages of unconsciousness and up to the time of expiration. These are fasciculations and myoclonic movements of the palate and related structures which have been known to be due to lesions of one inferior olive and opposite dentate nuclei. Generalized rigidity has been noted by us in one patient rendered unconscious by Thorazine and in one patient overcome by illuminating gas. Flaccidity of the limbs were observed often in deep stages of coma, but preservation of muscle tone was found to exist just prior to expiration. In cases of overwhelming cerebral hemorrhage the limbs may be spastic up to the moment of death. In situations where the limbs are spastic on one side and flaccid on the other, errors in predicting laterality were significantly great. In the latter cases both sides of the CNS were often involved.

## PART II. TWO SPECIAL TESTS FOR EVALUATION OF UNRESPONSIVE STATES

### Oculo-Cephalic and Vestibulo-Ocular Reflexes

In addition to the foregoing methods of evaluating unconscious states, we employ techniques which aid us in determining 1) whether a given unresponsive state is psychogenic or organic, 2) the depth or stage of unconsciousness, and 3) the integrity of extra-ocular movements. We have found that the routine methods have not always been reliable indicators of the stage of unconsciousness and vary greatly from patient to patient. Also it is well known that in unresponsive psychogenic states such as catatonia, reactions to painful



stimuli and the corneal reactions may be absent. We have investigated and used two tests that have been added to our routine procedures for all patients admitted in responsive states: The oculo-cephalic reflex and the oculo-vestibular reflex as elicited by cold caloric stimulation.

### The Oculo-Cephalic Reflex

The oculo-cephalic reflex ("doll phenomenon") is an easy and reliable method of testing the integrity of extra-ocular movements in patients with altered states of consciousness.



FIG. 1. Oculo-cephalic reflex. In this instance, the head is passively turned to the right and the eyes are in conjugate deviation to the left. This is a normal oculo-cephalic response.

In the normal *awake* subject, this reflex consists of conjugate deviation of the eyes while fixing a target and turning the head. Even when fixation of a target is not possible, as in total darkness or unconscious states, rapid passive turning of the head results in contralateral conjugate deviation of the eyes opposite to the head movement (Fig. 1). Similarly, rapid flexion and extension of the head will result in opposite vertical deviation of the eyes. This maneuver is not employed frequently because of the limitation in range of extension in comatose patients.

The oculo-cephalic reflex in the unconscious patient is elicited by holding the eyelids open and rapidly turning the head to one side and then to the other. If the eyes are observed to move conjugately opposite to the head movements, the reflex is intact (Fig. 1). This reflex is commonly present in lighter stages of unconsciousness and disappears in deeper stages. When the reflex is

absent the eyes fail to move from the mid-position despite the change in head position. With this maneuver, a nystagmus is often elicited on lateral gaze which may be the only clue to barbiturate intoxication or brainstem dysfunction from other etiologies. An oculo-cephalic reflex that is *intact* in one direction and *absent* in the other direction suggest paresis or paralysis of conjugate gaze to one side and may be of localizing value. In addition, the elicitation of dyseconjugate eye movements by this maneuver is usually associated with a brainstem lesion or an ocular nerve paresis. For example, one eye may abduct while the other eye remains in the mid-position, suggesting the syndrome of



FIG. 2. Oculo-vestibular response. This subject demonstrates the tonic deviation of the eyes to the side of stimulation as would be found in the unconscious patient with cold caloric stimulation of the right ear.

the median longitudinal fasciculus. We have yet to encounter an absent oculo-cephalic reflex in a patient subsequently proven to be a catatonic schizophrenic.

### The Vestibulo-Ocular Reflexes

The vestibulo-ocular reflex is elicited by cold water stimulation of the ear canal in the normal *awake* subject which produces the characteristic responses of coarse horizontal nystagmus in all gazes, most pronounced on gaze in the direction opposite the side of stimulation. The nystagmus has a quick and slow component; quick in the direction away from the side of stimulation and slow toward the side of stimulation. In addition, the subject veers and past-points to the side of stimulation. Commonly, there is associated nausea and autonomic

reaction. Until recently, relatively little use has been made of the cold caloric test in patients with altered states of consciousness.

The method of stimulation is simple. A standard 30 or 50 cc syringe with rubber or polyethylene tube attached, iced water and an emesis basin are all the equipment required. The iced water is syringed slowly and steadily into the ear canal for three minutes, unless an ocular response is observed before

**PATTERNS OF OCULAR MOVEMENTS FROM WAKEFULNESS TO DEEP COMA  
AS A RESULT OF CALORIC STIMULATION**









WAKEFULNESS	CALORICS		O - C
	S		
			PRESENT
			PRESENT
			ABSENT
			ABSENT
DEEP COMA			

FIG. 3. S = side of stimulation;  $\rightleftharpoons$  = nystagmus. The column on the right (O-C) represents the oculo-cephalic reflex.

then. Our arbitrary period for maximum stimulation is three minutes. If there is no response by this time, we are assured that the reflex is absent. Excessive impaction of wax may occasionally alter the response, and if no response is produced the wax should be removed and the test repeated (Fig. 2).

We find that there is a predictable pattern of ocular responses to cold caloric stimulation from wakefulness to deep coma. Several groups of patients were studied: A) normal subjects with altered states of consciousness induced by drugs (barbiturates); B) patients admitted in deep coma from overdose of drugs (usually barbiturates); C) patients undergoing general anesthesia for

abdominal operations; and D) patients with psychogenic disorders, such as catatonic schizophrenia, and E) normal subjects under deep hypnosis.

The ocular response of groups A, B, and C revealed *four* distinct, predictable stages from drowsiness to deep coma (Fig. 3).

**Stage 1.** Cold calories produce arousal with normal ocular responses as seen in wakefulness, that is, quick and slow phase nystagmus, most apparent on gaze opposite to the side of stimulation, somewhat less on direct forward gaze, and least apparent on gaze to the side of stimulation. This was associated with transient arousal.

**Stage 2.** Cold calories produce tonic conjugate deviation of the eyes to the side of stimulation *with* a fine nystagmus. It is often difficult to determine the quick and slow phase of this fine nystagmus with the naked eye, but by means of electronystagmography we were able to confirm that the quick phase is *away* from the side of stimulation and the slow phase toward the side of stimulation.

**Stage 3.** Cold calories produce tonic conjugate deviation of the eyes to the side of stimulation *without* nystagmus.

**Stage 4.** (Deep coma) Cold calories produce *no* ocular response, the eyes remaining in or near the mid-position.

In group D (unresponsive patients due to psychogenic disorder), the ocular responses to cold calories were those of typical wakefulness, despite the lack of reaction to painful stimuli and absent corneal reflexes. On the other hand, four patients known to have periods of catatonia and previously institutionalized for schizophrenia were examined in the emergency room and initially suspected of being in another catatonic state. Cold calories gave tonic ocular deviation to the side of stimulation without nystagmus. Further investigation disclosed that two of the patients had subdural hematoma, one subarachnoid hemorrhage, and the other barbiturate poisoning.

Two subjects with no neurologic deficits were hypnotized to the stage where by suggestion pin prick to the face and corneal stimulation elicited no response. Further suggestion was given that the eyes would remain staring directly forward and would not move no matter what the stimulus. Cold caloric stimulation produced prompt typical normal ocular nystagmus, although the subjects were still under hypnotic trance. These experiments corroborated the great resistance of the oculo-vestibular reflex.

## SUMMARY

In summary, the oculo-vestibular response to cold caloric stimulation aids in determining whether an unresponsive state is organic or psychogenic. It is a reliable indicator of the depth or stage of organically acquired unconsciousness, and when used serially is a good indicator of the patient's progress. As with the oculo-cephalic reflex, the elicitation of dissociated ocular movements suggests dysfunction of the brainstem and/or its oculomotor or vestibular projections.



# Auscultation, Palpation and Compression of the Neck and Head

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The simple acts of applying the stethoscope or the examiner's hands to the neck and head of the patient are usually not included in the routine examination. This is unfortunate since information of diagnostic importance can sometimes be obtained from these maneuvers. They are neither time consuming to the physician, nor with the possible exception of compression of the arteries of the neck, uncomfortable or harmful to the patient.

## Auscultation

The stethoscope, for many years an addendum to the neurologist's armamentarium largely employed for the recognition of intracranial vascular malformations, has only recently become an essential part of the neurologist's equipment for the diagnosis of extracranial occlusive vascular disease.

## Technique

Auscultation of the neck is best performed with the bell, rather than the diaphragm, of the stethoscope. The examiner routinely should listen to both carotid arteries as low as possible, in the middle positions of the neck, and at the angles of the jaw. Only gentle pressure should be exerted on the arteries, as too forceful an application of the stethoscope can create bruits where none exist. It is helpful to have the patient extend his neck and hold his breath during the periods of auscultation. The necks of uncooperative patients with noisy respirations can frequently be auscultated if the examiner closes the patient's mouth.

In addition to listening to the carotids, an attempt should be made to hear the subclavian and origin of the vertebral arteries in the supraclavicular fossae. Vertebral artery bruits may occasionally be heard by auscultation of the posterior portion of the neck. Rotating the patient's head to either side may sometimes bring out bruits which are not audible with the head straight. The evaluation of patients with neurologic symptoms possibly due to a thoracic outlet syndrome should include auscultation in the supra- and intraclavicular regions while the arm is abducted and the head rotated away.

If a bruit is heard in the neck the examiner should note if it is unilateral, particularly after exercise, its duration and pitch, its intensity as the stethoscope is moved closer to and away from the base of the heart, and its possible transmission over branches of the external carotid (especially to the mastoid region) or to the eye and head. The effects of compression of either carotid artery below a unilateral bruit should also be determined.

Auscultation of the head is also performed with the bell. The mastoid, temporal, parietal and frontal regions should be examined. The eye globe is ex-



amined with the patient looking at an object with his other eye to minimize the noise induced by blinking. Attempts should be made to abolish an ocular or cranial bruit by compression of the carotid artery in the neck.

### Interpretation

The presence of a neck or head bruit does not by necessity indicate neurologic disease. Head bruits have been reported in 60 per cent of normal children at four or five years of age. A "venous hum" is also a normal finding in older children or adults. The "venous hum" at the base of the neck can be abolished by compressing the neck vein above the hum. Neck and head bruits can be heard in patients with severe anemia, hyperthyroidism, Paget's Disease, glomus tumors, intrathoracic vascular malformations, intraorbital angiomas, and possibly other non-neurologic conditions. A localized bruit in the middle portion of the neck may be related to a highly vascularized thyroid.

The most frequent cause for neck bruits in patients of the age group when cerebrovascular disease is common is not a local stenotic lesion but rather the transmitted murmur of aortic stenosis. This can usually be distinguished from the bruit of a local carotid stenosis by its bilaterality, the increased intensity as the base of the heart is approached, and the similarity of timing and pitch of the cardiac and neck murmurs. The bruit due to local carotid disease is said to occur later in systole than the aortic murmur. If both carotid and aortic stenosis are present in the same patient, the bruit of the carotid lesion may still be recognized in addition to its timing in the cardiac cycle, by its different quality from the basal murmur, its unilaterality, and its increased intensity at the angle of the jaw or region of the thyroid cartilage. Even the murmur of aortic stenosis may be of some diagnostic aid. This murmur may be transmitted to only one carotid if the other carotid is completely obstructed. A neck bruit can also be heard over a perfectly patent vessel if increased flow in that vessel is responsible for collateral circulation in the distribution of another occluded vessel. Unilateral bruits have thus been heard over the patent carotids of patients with contralateral complete carotid occlusions.

A localized, unilateral systolic neck bruit, with the characteristics described above, is strong presumptive evidence for a local stenotic arterial lesion. However, this may or may not be related to the patient's neurologic symptoms. The bruit, for example, may be due to narrowing of the external carotid artery, rather than the internal. Stenosis of the internal carotid artery may also be present in neurologically asymptomatic patients. Moreover, the neck bruit may sometimes exist on the side opposite to cerebral vascular lesion.

The final evaluation of a unilateral neck bruit, therefore, requires consideration of the entire clinical picture. We do not believe that a definitive diagnosis of symptomatic partial arterial obstruction can be made by auscultation alone.

The bruits heard in the neck due to stenotic lesions of large arteries are usually systolic. On the other hand, the bruit heard in the neck or head due to arterio-venous fistulae are usually continuous. In our opinion, there is little localizing value to the site of a head bruit due to an intracranial vascular malformation, with the possible exception of laterality. Head bruits have been ob-

served in certain vascular cranial or intracranial neoplasms, particularly hemangiomas and rarely meningiomas.

Eyeball bruits are almost always present with traumatic cavernous-carotid fistulas and sometimes with intracranial malformations. The bruit of carotid stenosis in the neck is rarely transmitted to the eyeball. Despite statements to the contrary, we have never heard an eyeball bruit with a proven stenotic lesion of the carotid siphon. We have heard, however, eyeball bruits due to a patent carotid supplying collateral circulation to the distribution of a contralaterally occluded carotid.

### **Palpation**

While auscultation over the carotid may suggest partial occlusion, palpation of the carotid pulse is rarely of diagnostic aid even if a complete internal carotid occlusion is present. This is true, in our opinion, both for palpation of the pulse in the neck and for intraoral palpation of the pulse in the pharynx. The quality of carotid pulsations is of diagnostic aid only with the rare occlusion of the common carotid artery which results in a loss of not only the carotid pulse in the neck but also the superficial temporal artery pulse. Unequal carotid pulsations may also be due to other conditions including aortic arch aneurysm, double aortic arch, atypical coarctation, and cervical rib syndromes.

A palpable thrill can sometimes be felt over a stenotic carotid lesion but this never occurs without an audible bruit.

Palpation of the skull may rarely be of diagnostic aid. A localized thickening or bulge may be indicative of a meningioma growing through the inner table, myeloma, or metastatic cancer. Depressed skull fractures can sometimes be felt and increased intracranial pressure suggested by the tension in the fontanelle of infants or in the bone flap in patients with previous craniotomy. Percussion of the skull of infants and children with elevated intracranial pressure is said to produce a "cracked pot" sound but this finding must occur more often in textbooks than in patients.

Palpation in the neck at the region of the carotid sinus may provide symptoms of the well known "hyperactive carotid sinus syndrome." These may include syncope and convulsive seizures which occur within a few seconds of carotid sinus stimulation. These effects are usually associated with asystole, a significant bradycardia, or drop in blood pressure. The responses associated with changes in pulse rate may be prevented by administering atropine 0.4 milligram intravenously prior to carotid sinus palpation. The effects associated with hypotension may be prevented by administering vasopressors or by injecting Novocain into the carotid sinus. These maneuvers may, at times, be required to distinguish the responses resulting from carotid sinus hypersensitivity from those due to manual compression of the carotid arteries.

### **Compression of the Carotid Artery**

#### **Technique**

The examiner faces the patient who sits erect and extends both arms. The examiner places the fingers of one hand as low on the patient's neck as will allow

carotid pulsations to be felt clearly. Firm pressure is then exerted against the transverse processes of adjacent vertebrae. The adequacy of compression is checked by palpating the ipsilateral superficial temporal pulse which should be obliterated if compression is satisfactory. Compression is maintained for up to thirty seconds unless the patient begins to show a downward drift of one extended arm, loses consciousness or has a seizure, at which time compression is immediately discontinued. Eye movements and speech can be evaluated during the period of compression. A meaningful test requires independent compression of both carotids. Compression with the head turned to either side can also be employed.

A positive test is one which induces any one or more of the following: an extremity drift, syncope, or seizure either focal or general. After the compression there may be contralateral paresthesias. A negative test is one which does not produce these signs after thirty seconds of compression. Symptoms of paresthesia in the extremities or dizziness are not considered indicative of a positive response.

### **Interpretation**

The positive response to carotid compression takes several seconds to occur in contradistinction to the almost instantaneous effects of a hypersensitive carotid sinus. The two responses can also be separated by monitoring the pulse rate and blood pressure and by the prior administration of medication.

A positive test by itself is not diagnostic. Bilaterally positive responses are sometimes noted in elderly patients without known neurological disease. A unilateral response, however, may suggest a contralateral carotid occlusion, or at least that both anterior cerebral arteries are supplied by the compressed carotid. A test which becomes positive when the patient's head is rotated may indicate vertebral artery obstruction by cervical osteophytes. The presence of vertical nystagmus during compression is suggestive of vertebrobasilar insufficiency.

This test is also useful in evaluating patients for various types of carotid surgery and its results should always be known prior to carotid arteriography.

Information can sometimes be obtained without producing syncope or seizures. Headaches of vascular origin, as in migraine, can usually be abolished by carotid compression. Simultaneous carotid compression with auscultation and/or ophthalmodynamometry may be of help in the recognition of extracranial occlusive vascular disease.

The procedure is not without risk. Fortunately, with careful technique complications are extremely rare. The information to be gained from the proper performance of carotid compression generally outweighs the possible risk.

### **SUMMARY**

There is indeed a variety of diagnostic information to be gained from auscultation, palpation and compression of the neck and skull. These maneuvers, however, cannot establish a definitive diagnosis by themselves. They are of aid to the physician only when considered with the entire clinical picture. At times they may also suggest the need for further diagnostic procedures.

# The Use of Sodium Amytal for Testing Mental Function

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Studies over the past fifteen years have demonstrated the value of using amobarbital sodium (amytal sodium®) as a diagnostic test for the presence of brain damage (1). Under the influence of this drug, certain changes in orientation for time, place, person and awareness of illness occurred in patients with brain disease which did not appear in persons without demonstrable brain pathology. Originally, the idea for the Amytal Test came from the observation that when these phenomena had cleared in the course of clinical improvement they could again be elicited by the administration of barbiturates.

**Patterns of Disorientation.** To understand the rationale of the procedure it is necessary to review briefly the patterns of disorientation and denial of illness that are seen in association with brain injury. While gross disorientation for place and time is readily recognized, the various patterns of partial disorientation are less well recognized (2).

In disorientation for place, the patient may misname the hospital, giving it the name of another hospital or some nonexistent place. He may use a euphemism such as "sanitarium" or "repair shop." He may name the hospital correctly but locate it in another city or another part of the city. The change in locale is generally to the patient's home or place of occupation. Or, the patient may name and locate the hospital correctly but greatly condense the distance between the hospital and his home. Thus a patient who lives several miles away may say he can see his home through the hospital window. Another pattern of disorientation is the so-called confabulated journey in which the patient, when asked what he has done, confabulates having gone home or on a shopping trip.

Another pattern of disorientation is the reduplication of the hospital. The patient may say that there are two or three Mount Sinai Hospitals, locating one correctly and the "other" elsewhere. Commonly, patients say that the fictitious Mount Sinai is a "branch" or "annex" of the original. Another form of reduplication is a statement that a hospital and a hotel or housing project are all in the same building. There may be temporal reduplication in that the patient says that he has been in the hospital previously, when in actuality he has not.

**Time.** Disorientation for time is expressed by errors in the year, month, and time of day. Under hospital conditions patients without demonstrable brain disease made errors in the time of day but these did not cross a meal time. Only in patients with organic involvement were morning and afternoon, afternoon and evening, or day and night reversed. Some patients with brain disease give the correct hour but reverse A.M. and P.M. It is characteristic of patients with brain disease who are disoriented for time to remain so, even though a clock with the

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correct time is in ready view. Patients with brain disease also make errors in the year and month which are not present in control groups, though errors in the day of the month may occur in both groups. Disorientation and reduplication for person may be expressed by the patient misidentifying the examiner or fabricating a story that he had seen him in some other place.

**Denial of Illness.** Denial of illness, or anosognosia, is common among patients with organic brain disease. Thus a seriously incapacitated person may say he is well and deny such disabilities as hemiplegia, blindness, diplopia, headache, vomiting, incontinence, and the fact that an operation has been performed. The denial may be expressed in delusional fashion or in an evasive "I don't know." Frequently, the patient states that he came to the hospital for some minor complaint such as "constipation," or for a "check-up." The symptoms of illness and even the ownership of a paralyzed arm may be attributed to others. Or, a patient may place the disability in the past and maintain that he is quite well at present.

### Test Procedure

The Amytal Test is considered positive for the existence of brain disease when, under the influence of the drug, there are manifestations of *change* in orientation and awareness of illness in persons who, prior to drug administration, were oriented and expressed awareness of illness.

**Questions.** The patient is instructed that he will receive an injection that will test his memory and reactions. He is asked to lie down and the following questions are asked:

1. What is your main trouble?
2. Why did you come here?
3. What is the full name of this place?
4. Where is it located?
5. How far from here do you live?
6. Have you been here before?
7. Have you been in any other Mount Sinai Hospital?
8. What did you do last night?
9. What is today's date?
10. What time is it now?
11. Who am I?
12. Have you seen me before coming here?

**Injection.** After the questions and answers are initially recorded (it is suggested that they be tape recorded) the injection is begun. The drug is given intravenously in a solution of 0.5 Gm in 10 cc of water at a rate of .05 Gm per minute. As the drug is being administered the patient is asked to count backward from 100 to one. The injection is continued until the patient makes errors in counting, shows nystagmus on lateral gaze, and has slurring of speech. Some drowsiness is generally present at this point and all of these manifestations are regarded as physiological indicators of drug action. The effect is generally reached after the administration of 0.2 to 0.4 Gm, and the questioning is re-



sumed at this time with the same questions used in the pre-drug interview. When an error is made the question is repeated, as it has been found that normal subjects, *i.e.*, those without brain disease, may make transitory errors. Both the preliminary questioning and answers and the interview after drug administration are recorded verbatim. If a positive result is not obtained after the giving of sufficient drug to produce a physiological reaction, there is no advantage in injecting more of the solution. Some problem is created by subjects who appear drowsy. If they cannot be roused to make a response, then no conclusions can be drawn. Before a test is considered negative, the list of questions is repeated as occasionally a 1+ response may be obtained after the patient has answered the initial round of questions without significant change.

**Scoring.** The scoring is done on the basis of the total errors made. One error is graded as 1+, two or three as 2+, four or five as 3+ and more than five is rated 4+. It is important that the criterion of *change* be maintained. The test is not of value with subjects who in the preliminary questioning deny illness, express disorientation, or who are not communicative. These manifestations are generally not greatly altered by the drug. If a subject originally says that he came for headaches and then after injection says, in reply to the same question, "I don't remember" or "what do you mean" consecutively, this is a positive response. Some modification in the questions may be made. For example, if a patient is already disoriented for place, he is not asked if he has been in another Mount Sinai Hospital; or if he spontaneously confabulates about the examiner, he is not asked to identify him. Actually, it is not necessary for a response to be wrong to be scored as positive. Thus, under the effects of a drug a patient may state that he came to the hospital because his doctor said he should be admitted. If his original answer is that he came for headaches or trouble in walking, then the response is significant. The factor of *change* is the significant point.

Certain errors are made by control groups and are not specific for brain disease. One of these is a slight change in the address or name of the hospital. While the Mount Sinai Hospital is situated between 97th and 101st Street between Fifth and Madison Avenues, a normal subject may be incorrect in locating it at 100th Street and Park Avenue or Fifth Avenue and 105th Street. The name of the hospital may be qualified, as "The great Mount Sinai Hospital with the most stupendous doctors," or, when asked to identify the examiner, the patient may refer to him as a "big wheel doctor." The date may be given as the 19th or 20th of the month. Such errors may also be made in the pre-drug questioning.

## Results

**Positive Results.** Our findings indicate that the occurrence of a positive Amytal Test depends not only on the presence or absence of brain disease per se, but on the location, extent, type of onset and rapidity of progression of the pathological process. The highest incidence of positive results occurred with rapidly developing, deeply seated and diffuse lesions. These conditions are fulfilled by infiltrating or metastatic neoplasms, acute vascular, traumatic and inflammatory lesions, bilateral pre-frontal lobotomy, tumors in the region of the

third ventricle, and pre-senile dementia. When the test is negative in cases of brain tumor, the lesion is often benign and superficial such as a meningioma of the convexity. The low incidence in seizure cases is due to the fact that usually no evidence of brain damage could be found apart from the EEG abnormality. The relatively low incidence following head injury reflects the circumstance that most cases were tested many months after the initial trauma. The 50 per cent incidence in degenerative and demyelinating diseases indicates the extent of the pathology and, particularly, the rate of progression. While patients who later were proved to have pre-senile dementia generally yielded positive results, patients with Parkinson's disease or multiple sclerosis in remission were usually negative. The importance of activity was shown when a negative result was obtained in two patients who had had right hemisphereectomies for old atrophic lesions.

**Special Value.** The test has been particularly useful in patients with brain tumor or other progressive pathology in whom there are no focal or lateralizing signs or manifestations of increased intracranial pressure, and in whom the symptoms have been changes in mood, work efficiency, and social behavior. It has also been helpful in distinguishing central from peripheral lesions, and in cases where there is known malignancy and the question of intracranial metastasis has arisen. Another advantage is that the preliminary questioning involves a systematic examination of the patient in an area where observations are often haphazard. Frequently we have been asked to do an Amytal Test on a patient who is already disoriented.

**Reliability.** The test results have been consistent in that if the procedure is repeated in a few days a positive score usually remains positive and a negative response persists. In one case of an old brain injury, where the symptoms consisted of chronic depression and irritability, 22 positive 1+ and 2+ results were obtained over a period of two years. However, the serial administration has been valuable in evaluating clinical change and prognosis. Thus clinical improvement and the clearing of neurological signs may be accompanied by a change from a positive to negative result or a shift from, say, a 3+ to a 1+ score. Conversely, what looks like clinical improvement may actually represent an increase in brain damage and this can be verified by the Amytal Test. For example, a patient who has been depressed and complaining may become unworried and euphoric with a change from a positive to a negative test. In the hospital the procedure has also been valuable in determining the time of discharge of patients who have had head injuries. It has been our policy not to advise discharge while the Amytal Test is still positive.

### ***Case Reports***

#### CASE 1

The patient was a 62 year old woman who, four years previously, had sustained a severe brain injury in an automobile wreck. She was reported as having been unconscious for several weeks and as confused for several months. In her con-

fusion she was said to have been euphoric, paranoid, and as showing "uninhibited sexual behavior." Following her release from the hospital she became irritable, depressed and complained of pain in her perineal region. Neurological study showed no intellectual deficit and she was regarded as a case of psychogenic depression with sexual conflicts. The following test was done in a private sanitarium where she was taken after a suicidal threat.

*Pre-Drug Interview*

*What is your main trouble?*

There's something up there between my rectum and uterus.  
Pain, throbbing.

*What is the full name of this place?*

Huntly Manor Sanitorium or arium.

*Where is it located?*

0000 Alaska Avenue. (Correct)

*Have you been here before?*

No.

*Is there any other place by this name?*

Not that I know of.

*What did you do last night?*

I visited a little old lady; she's in a terrible mess.  
Watched T.V.

*What is today's date?*

March 15, 1960. (Correct.)

*What time is it now?*

Four o'clock. It's all right if I look at my watch, isn't it? (Correct.)

*What is my name?*

Dr. Edwin Weinstein.

*Post Drug Interview*

She was given 0.35 Gm of amytal sodium. She became slightly drowsy after 0.15 Gm, errors in counting appeared consistently after 0.2 Gm and nystagmus was noted at 0.25 Gm. Tests repeated at monthly intervals over the next year consistently yielded 1+ and 2+ positive results.

*What is your main trouble?*

My ass hurts if you want to know.

*What is the full name of this place?*

Hunamasset Manor Sanitorium.

*What is the name of this place?*

Huntly Manor Club.

*Where is it?*

0000 Alaska Avenue.

*What did you do last night?*

Watched T.V.

*What is today's date?*

September 15, 1960.

*What time is it now?*

Must be about 4:30.

*Morning or afternoon?*

Afternoon. I was asleep in the morning.

*What is my name?*

Dr. Edwin Weinheim; I mean Weinstein.

This test was scored as 2+ positive on the basis of disorientation for place and disorientation for date. The more colloquial way in which the patient referred to her rectal pain was not considered significant.

## CASE 2

The following exemplifies a positive amytal test in a 44 year old naval serviceman. There was a two year history of fatigue, gastrointestinal complaints, and diminished efficiency in his work. An electroencephalogram had been reported as normal and psychological tests had given no clear indication of organicity. He was tested on June 7, 1960, shortly after his admission to the National Naval Medical Center at Bethesda, Maryland.

### *Pre Drug Interview*

*What is your main trouble?*

Stomach aches, dark stools, feel tired, let down all the time.

*What is the full name of this place?*

Navy Medical Center, Bethesda Naval Hospital.

*Where is it located?*

Bethesda outside of Washington.

*Have you been here before?*

No.

*Have you been in any other hospital with this name?*

No.

*Now, how far is this place from your home?*

I live in Miami, that's where my wife is, 1400 miles.

*Do you know who I am?*

Yes, Dr. Weinstein. I think you said you were a consultant.

*Have you seen me before?*

I don't think so.

*What did you do yesterday?*

Laid around, watched T.V.

*What is the date today?*

Sixth or seventh of June, 1960.

*What time is it now?*

Must be around 3 o'clock. (Correct)

*Post Drug Interview*

He was given a total of 0.4 Gm of amytal sodium. Nystagmus appeared after .015 Gm. Counting errors were made early but were self-corrected until he had received .025 Gm. His voice became dysarthric at .035 Gm and he was moderately drowsy. The subsequent questioning was as follows:

*What is your main trouble?*

Getting out of this chicken outfit with money to swing what he wants to.

*What is your main trouble?*

Guess the desire to be 24 years old and I'm 44.

*What is the full name of this place?*

U.S. Navy (unintelligible).

*What is the full name of this place?*

Medical Center, Charleston.

*Where is it located?*

West and a little north.

*How far is your home from here?*

About 400 miles. (This is approximate distance between Miami and Charleston, S.C.)

*What did you do yesterday?*

Jumped around out there. Helped the boys dispose of things.

*What did you do?*

(Yawn.) Up the peninsula a little way running agricultural control for somebody.

*Do you know who I am?*

Head shrinker type. From St. Elizabeth's.

*Who am I?*

Head shrinker they say. From down the river.

*Ever seen me before?*

Nope.

*What's the date today?*

Seventeenth of June, 1958.

*What time is it now?*

2100 hours or a little later.

*What time is it?*

2100 hours.

On the basis of denial of illness, disorientation for place, a confabulated jour-



ney, disorientation for year, disorientation for time of day and misidentification of person, the test was scored as 4+ positive. Two years later the patient returned to the hospital. At this time he had a markedly abnormal electroencephalogram and a pneumoencephalogram showed marked dilatation of the ventricles indicative of brain atrophy.

### **Psychiatric Aspects**

The changes in language produced by amytal sodium have had psychiatric applications. The Amytal Test has been useful in the evaluation of the effects of electroshock treatment (EST), serving as an index of prognosis. In cases of depression and other mental illnesses treated with EST, patients who showed marked clinical improvement had a significantly greater number of positive amytal tests and developed positive results earlier in the course of treatment than patients rated as unimproved and only moderately improved. Moreover, the positive results came on earlier in the markedly improved group appearing after the third or fourth treatment. After the usual course of from eight to twenty-four treatments, the Amytal Test becomes negative with two weeks of the last convulsion.

The test has also been used systematically in patients hospitalized for mental illness with the aim of distinguishing subjects with affective psychoses from those with known structural brain damage (3). Of ninety people tested in a state hospital and a private psychiatric institution, there were six positive results, all 1+. In three of these subjects signs of organic brain disease were subsequently found.

While these results indicate that the procedure has diagnostic value, there are many methodological problems. Psychotic patients may deny that there is anything wrong with them even before the drug is given. In answer to the initial "main trouble" query, it is more difficult to formulate unhappiness and social alienation than it is some physical symptom. A number of schizophrenic patients are verbally uncommunicative and others refuse to take the test. In those who consent there are many indications of fear and distrust. Some patients refuse to lie down, some have to keep one foot on the floor. The procedure itself may become incorporated in a fear or delusion that the patient will be killed. About one-quarter of the mental hospital patients showed marked withdrawal during the test, refusing to answer questions for long periods or mumbling incoherently. This is a much larger proportion of withdrawal reactions than in the normal controls and is even somewhat higher than the incidence in the brain disease group.

### **Comment**

The action of sodium amytal is not fully understood and explanation involves physiological, perceptual, symbolic, and motivational factors. Operationally one is dealing with language and adaptation to stress. A useful formulation is the idea of an altered mode of interaction in the environment affecting the patterning of symbolic elements. Much of what is said to the patient is interpreted in a dif-

ferent context of language. When he mislocates the hospital to a place near his home he has not simply forgotten the correct address but is using the change in an idiosyncratic, selective fashion to express personal motives and preoccupations. The language represents not only deficits but adaptive processes. In both the brain diseased and normal groups, the adaptation involves the incorporation of symbolic elements into such socially organized idioms as clichés, puns, malapropisms, and stereotyped phrases. Although a common mode of action exists, the groups of brain-injured and normals can be differentiated on a quantitative statistical basis and herein lies the value of the Amytal Test as a diagnostic aid and research method.

#### REFERENCES

1. Weinstein, E. A., Kahn, R. L., Sugarman, L. A., and Linn, L.: Diagnostic Use of Amobarbital Sodium ("Amytal Sodium") in Brain Disease. *Am. J. Psychiat.*, 109: 889, 1953.
2. Weinstein, E. A., and Kahn, R. L.: Patterns of Disorientation in Organic Brain Disease. *J. Neuropath & Clin. Neurol.*, 1: 214, 1951.
3. Kahn, R. L., Fink, M., and Weinstein, E. A.: The "Amytal Test" in Patients with Mental Illness. *J. Hillside Hospital*, 4: 1955.

# **The Use of Sodium Amytal for Testing Visual, Sensory and Motor Function**

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The use of the sodium amytal as a diagnostic technique is not limited to discovery of changes in mental function or language although this was its earlier application. It has also been of value in eliciting perceptual and motor deficits that are inconspicuous or undiscovered on routine clinical testing. Existing deficits are accentuated and previous defects which have cleared may reappear.

## **Test Procedures**

The procedures are similar to the amytal language test in that the drug is administered in the same fashion and identical testing is performed before and after the drug is given. If the procedures are combined, the neurological examinations are done after the verbal questioning. The visual field examination is usually a brief one since patients may not be cooperative under the effects of the drug. Under these conditions, tachistoscopically presented pseudo-ischromatic plates have proven to be valuable.

Sensory testing is usually done by the method of double simultaneous stimulation and may be limited to testing by pin prick and touch. Other modalities may be tried but there is apt to be difficulty in securing enough cooperation to provide consistently reproducible results. In examining for motor defects, the patient is asked to extend his arms in supination with extended fingers. "Spoon-ing" or partial pronation and drift of the outstretched hand occurs if motor weakness is present. The drift is considered significant if the affected limb falls at least several inches. The Barré maneuver permits similar testing of the lower extremities.

## **Case Report**

A 49 year old right-handed man awoke on April 3rd to find his left arm "weak and uncontrollable;" there was improvement after several hours. On April 7th he again noted weakness of the left hand and had a grand mal seizure. Postictally he had a left hemiparesis and a left plantar extensor sign which cleared during the next few days. The rest of the neurologic examination was normal. Right carotid arteriogram and PEG showed some shift of the ventricular system to the left but was not diagnostic and did not serve to localize the lesion. EEG on April 9th showed asymmetry in parieto-occipital leads with more slow activity and increased voltage on the right. He was re-admitted on May 22nd because the EEG showed increased slow electrical activity over the right hemisphere. Neurological examination disclosed no field defect (to 2 mm red test object) or hemi-inattention. He had difficulty doing fine movements in the left foot. There was no sensory loss of touch, pin prick, position sense, stereognosis, figure writing, or two-point discrimination.

0.5 Gm of sodium amytal was injected intravenously on June 2nd until slight dysarthria and nystagmus appeared. Under these conditions, testing with 2 mm red test objects elicited a left temporal field defect. There was extinction of the left hand on both face-hand and leg-hand touch. Double simultaneous pin prick was extinguished on the left hand. There were bilateral errors in position sense and two point discrimination but other sensory modalities were intact. There was also drift of the left upper extremity. At operation on June 26th a reddish gray cystic tumor involving the right parietal lobe was found. Subsequently the patient died of pulmonary embolus and examination of the brain revealed a metastatic adenocarcinoma.

### Comment and Summary

This case illustrates the value of the procedure in eliciting a visual field defect and hemisensory loss contralateral to the lesion not evident under ordinary conditions of testing. It was of interest that no change in language resulted.

A systematic study by Teng and Bender (1) of 100 patients with intracranial and spinal cord disease illustrates the use of the procedure in eliciting motor defects. The most marked changes occurred in cases of brain tumor and cerebral vascular disease involving the motor area while no weakness was produced in tumors of the pituitary fossa and eighth nerve or in cases of multiple sclerosis without bulbar involvement.

The intravenous amytal test is a useful clinical diagnostic tool providing more clear cut evidence of perceptual and motor defects in patients with disease of the central nervous system. The temporary alteration of function induced by the barbiturate has permitted focal defects otherwise latent to become accessible for diagnosis and prognosis. The development of these focal signs may be the first evidence of localization and the presence of significant organic disease. The patient with clinical evidence of recovery may show recurrence of signs under amytal and the degree of functional impairment can thus be further assessed.

### REFERENCES

1. Teng, P. and Bender, M. B.: Effect of Barbiturates on Latent Motor Deficits. *Neurology*, 5: 777, 1955.

# The Hot Bath Test in the Diagnosis of Multiple Sclerosis

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In the two previous articles it was pointed out that intravenous injection of drugs (sodium amytal) may bring out deficits which are not manifest on routine examinations. Similarly, the elevation of body temperature may also bring out latent deficits.

Although the signs and symptoms of many diseases of the nervous system increase in number and severity when the body temperature is elevated, the effect is most marked in cases of multiple sclerosis. Nelson and McDowell stated that "... the appearance of multiple signs when the body temperature is elevated between 0.5 degree F. and 2.5 degrees F. speaks in favor of this diagnosis" *i.e.*, multiple sclerosis (1). At this institution induced hyperthermia (hot bath test) has been used as a diagnostic test for this disease for the past fifteen years.

## Diagnosis of Multiple Sclerosis

The diagnosis of multiple sclerosis is primarily a clinical one although laboratory and other studies are useful to exclude other entities. Two of the most important clinical criteria are:

1. A history of remissions and exacerbations frequently upon a background of chronic and/or progressive disability.
2. Signs and/or symptoms suggesting the involvement of multiple anatomic loci; *i.e.*, dissemination.

The hot bath test has its greatest value in uncovering such multiple areas of involvement. The following illustrates the performance and interpretation of the test.

## Case Report

A fifty-two year old man (unit #230162) was admitted to The Mount Sinai Hospital in September, 1963 because of progressive weakness of his right arm and leg. In 1958 he first noted easy fatigability of his right leg; in 1960 his right arm was easily fatigued; in 1962 he developed a limp and was having difficulty using his right hand.

The positive neurologic findings were a moderately severe paresis of the entire right arm and leg with increased deep tendon reflexes, a right Babinski sign, as well as defective gait and coordination on that side. No atrophy or fasciculations were noted. There was no facial weakness. Mental, cranial nerve, and sensory examinations were normal.

The initial clinical impression was that he had a lesion involving primarily the upper motor pathways but the precise location (spinal cord, brainstem, or

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cerebrum) was unknown. A left parasagittal cerebral lesion such as a meningioma was considered a distinct possibility.

All routine and special laboratory examinations were normal. These included: a CSF exam, skull and cervical spine x-rays, EEG, left carotid arteriogram, left brachial arteriogram, myelogram and myelencephalogram. Although the case was atypical for multiple sclerosis, the battery of normal studies suggested that possibility by exclusion, and a hot bath test was performed.

The patient was examined while reclining in an empty bath tub. His oral temperature was recorded. The entire neurologic examination was performed with special emphasis upon visual and oculomotor functions. The bathtub was then filled to the nipple line with tepid water. Gradually the bath temperature was increased until just within tolerable limits. Repeated oral temperature readings were taken. As his temperature increased, the neurologic examinations were repeated. For this patient, as for most, new positive findings appeared by 102° and were marked by 104°F. In fact, many tests can be terminated at a considerably lower temperature. The new findings appeared as follows:

**102°F—Patient complained of “blurred vision.” This was present only with the left eye when each was tested separately. Testing with 2 mm red targets did not reveal a visual field deficit. Marked horizontal nystagmus on both lateral gazes, left greater than right, was also present.**

**104°F—Complained of numbness in fingers of left hand and was unable to move right hand or leg. Visual testing now revealed a central scotoma in the left eye.**

The bathtub was then emptied and as the patient's temperature returned to normal the induced findings disappeared.

The central scotoma suggests an optic nerve lesion and in this patient is evidence of a disseminated process. The nystagmus suggests a posterior fossa lesion but since the motor findings might also result from such a lesion it cannot be used as definite evidence for dissemination. Since the left hand numbness could be the result of a brainstem or spinal cord process it also is not proof of multiple involvement. If, however, the initial clinical course had supported a spinal cord lesion, then both the central scotoma and the nystagmus would have supported a disseminated process. In summary, the positive “hot bath test” unmasked presumably asymptomatic lesions *which by the nature of their distinctly separate localizations support the diagnosis of multiple sclerosis.*

In selected cases the procedure can also be used to intensify and verify uncertain clinical findings. Thus, an equivocal Babinski sign in a patient with an apparent retrobulbar neuritis may become clearly positive with hyperthermia. An important clinical consideration is the possibility that an acute exacerbation in multiple sclerosis may be the result of a treatable infection and its accompanying febrile response. Another interesting observation which also has possible therapeutic implications is the finding that mild hypothermia can produce significant (but only transient) clinical improvement in multiple sclerosis (2).

### **Mechanism of the Hot Bath Test**

The mechanism of the hot bath test is unknown. The following considerations however, suggest a possibility. A central scotoma is a common finding in multiple sclerosis and is believed to be due to an optic nerve lesion. Not infrequently this sign may only become manifest during induced hyperthermia. It would appear that the lesion, though present, can be asymptomatic at the usual body temperature. Consequently, whatever the mechanism responsible for the hot bath test is, it may operate in nerve fibers (optic nerve in this case) and may not necessarily directly involve synapses or complicated neural circuitry. Since the only known physiologic function of a nerve fiber is the conduction of impulses it seems reasonable that this process may somehow be altered. In support of this, recent experiments with a single isolated nerve fibers by the author (to be published) have shown that impulses are able to "jump over" small lesions at one temperature, but fail to do so at very slightly higher temperatures.

### **REFERENCES**

1. Nelson, D. A., and McDowell, F.: The Effects of Induced Hyperthermia on Patients with Multiple Sclerosis, *J. Neurol. Neurosurg. & Psychiat.* 22: 113, 1959.
2. Watson, C. W.: Effects of Lowering of Body Temperature on the Symptoms and Signs of Multiple Sclerosis, *New Eng. J. Med.*, 261: 1253, 1959.

## Neuroendocrinology

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Neuroendocrinology is the study of the interrelationships between the functions of the central nervous system and the endocrine organs. Clinically this discipline is in its infancy although its physiologic counterpart is relatively well developed.

Anatomic and physiologic studies have provided the basic concepts of these interrelationships. In essence, the limbic system or visceral brain (anterior temporal lobe, amygdala, hippocampal system, fornix, septal area) has been shown to have a two-way (or reciprocal) anatomic and physiologic relationship with the hypothalamus. There are also reciprocal anatomic pathways connecting the hypothalamus with the brainstem and spinal cord. These ascending and descending pathways converge and their effects are integrated in the hypothalamus which contains secretory neurons in many ways analogous to the anterior horn cells of the spinal cord. That is, these secretory neurons are a type of final common pathway, the chemical products of which are secreted into blood vessels instead of at neuromuscular junctions.

These secretory neurons are of two types. One produces chemicals (so-called *releasing factors*) which are secreted into special portal blood system and carried by it from the hypothalamus to the anterior pituitary. Here these various releasing factors act to result in secretion of the various trophic hormones, there apparently being one releasing factor for each trophic hormone. The trophic hormones in turn excite the appropriate target organs of the endocrine system. The secretory products of the various endocrine glands in turn act on the hypothalamus and possibly on other parts of the central nervous system in a regulatory capacity. For example, the cerebrum may excite the hypothalamus which excites the release of ACTH from the pituitary. This activates the adrenal cortex, some of the products of which act to dampen the hypothalamic release of corticotropin releasing factor and thereby reduce ACTH release.

The second type of hypothalamic secretory neuron has its cell body in the anterior hypothalamus (supraoptic nucleus) while its axon ends in the posterior pituitary. Secretory granules (probably ADH or antidiuretic hormone) are formed in the cell body, pass down the axon, and are stored in the ends of the axons in the posterior pituitary gland from which ADH is secreted in response to the appropriate stimulus.

The clinical expressions of derangements in this complex nervous-endocrine

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integration system are in the early stages of definition. For the neurologist, these derangements may be considered under four headings:

1. Cerebral dysfunction leading to endocrine dysfunction.
2. Hypothalamic dysfunction leading to endocrine dysfunction.
3. The pituitary-chiasmatic syndrome.
4. Endocrine dysfunction leading to central nervous system dysfunction.

Each of these categories will be briefly described in regard to central nervous system symptoms and endocrine symptoms. The appropriate clinical or laboratory tests available for each disorder will be indicated. The tests of endocrine function will also be summarized in tabular form (Table 1).

**Cerebral diseases** leading to endocrine disorder are at present poorly defined. In our laboratories we have recently shown that the circadian\* patterns of plasma 17-hydroxycorticoids may be abnormal in disease of restricted parts of the nervous system. Circadian variation in plasma 17-OHCS is a normal and stable phenomenon for the most part under control of the central nervous system. Disease in the temporal lobe and limbic system may disrupt the patterns of daily variation in the plasma 17-OHCS. This disruption may be the only indicator of endocrine dysfunction in patients with disease in these areas (see circadian variation in plasma 17-OHCS below).

**Hypothalamic syndromes** also present varying combinations of neurologic and endocrine dysfunctions. The particular symptoms vary in part with the area of the hypothalamus affected as well as with the etiology of the disease.

The more common symptoms of hypothalamic disease are: visual field changes indicating chiasmatic or even optic tract disorders, seizures, syncope, somnolence, anorexia, obesity and hyperphagia, sleep disturbances, temperature disturbances, diabetes insipidus, changes in libido and menses, disruption of the plasma 17-OHCS circadian patterns, and precocious puberty (see below).

Tumors of the hypothalamus and the third ventricle, in addition to local destruction, can alter intracranial pressure and produce the symptoms and sign of hydrocephalus. Masses (including granulomas) of the interpeduncular fossa can affect the hypothalamus, as can parasellar aneurysms of the internal carotid artery. On rare occasions the hypothalamus may be the major site of a viral encephalitis.

The patient with signs and symptoms suggesting hypothalamic disorder should be studied with lumbar puncture, arteriography, pneumoencephalography, and electroencephalography. The following determinations should be made: 17-ketosteroids, corticosteroids, estrogens, protein bound iodine, thyroid stimulating hormone, gonadotropins, electrolytes, and Hickey-Hare test for diabetes insipidus.

*Precocious puberty*, especially in males, may occur in posterior hypothalamic and/or pineal disease, especially tumors. In the course of such tumors, precocious puberty may be associated with symptoms of a deep midline space-

\* A circadian pattern is formed by a sequence of events or laboratory values which repeats itself every twenty-four hours.

TABLE I  
Available Tests of Endocrine Function

Clinical State	17 Keto-steroids	Cortico-steroids	Estrogens	P B I	Gonadotropins (pituitary)	Serotonin (SHIAA)	Sodium	Potassium	Calcium	Other Tests
Acromegaly	N to L	N		N or H	L or N		N to L <sup>+</sup>	N to H	N	H insulin tolerance
Addison's disease	L	L		N to L			N to H*			Water load test less than normal
Anorexia Nervosa	N to L	L	L	N to L	N to L	H				
Carcinoid	L			L						H Cholesterol
Cretinism										L BMR
Chromophobe Adenoma	L	L		L	L					
Cushing's disease	N to H	N to H	N to H	H	N to L		N to H	N to L	H <sup>o</sup>	H insulin tolerance test
Grave's Disease									I <sup>+</sup> <sup>o</sup> H <sup>+</sup> <sup>o</sup>	H inorganic phosphorus
Hypoparathyroidism				H						BMR—H TSH—H
Hyperparathyroidism										LATS—H T <sub>3</sub> —H
Hyperthyroidism				L						BMR—L TSH—L
Hypothyroidism										T <sub>3</sub> —L
Pheochromocytoma										Catecholamines*—H
Simmond's Disease	L	L	L	L	L		N to L <sup>+</sup> N to H*			Vanillyl Mandelic Acid*—H

+ serum.

\* urine.

<sup>o</sup> balance study.

N = Normal; H = High; L = Low.



occupying mass including papilledema, paresis of upward gaze, loss of pupillary light reflex, vertical nystagmus, and various parts of the hypothalamic syndrome (see above). In the course of adrenal tumor, adrenal hyperplasia or ovarian tumor associated with precocious puberty there are no central nervous system signs or symptoms.

*Aldosterone excretion* in the urine may be disturbed in disease of the posterior hypothalamic-pretectal area. This may be demonstrated by aldosterone determinations and by evaluating the degree of the rise in aldosterone in response to salt restriction.

There are three special tests available to aid in assessing pituitary-hypothalamic function. These are:

a) *Metopirone® (SU-4885) Test*: This drug, by damping the feedback control of ACTH production, should lead to a rise in urinary 17-OHCS provided the pituitary, hypothalamus and adrenal cortex are normal. If the latter is normal (as shown by ACTH test) and there is no rise in urinary 17-OHCS upon Metopirone administration, pituitary hypothalamic disease may be suspected. In our experience, the Metopirone test becomes positive only after other indices of hypothalamic dysfunction indicate abnormality and so is of limited value.

b) *Dexamethasone Suppression Test*: This drug leads to a fall in adrenocortical activity by suppressing the hypothalamic mechanism leading to ACTH production. If ACTH production is autonomous, as in physiologically active hypothalamic, pituitary, or adrenal tumors, Dexamethasone suppression does not occur. To evaluate the meaning of this test the function of the adrenal cortex must be fully assessed. We have found this test of doubtful value in arriving at a diagnosis of central nervous system disease.

c) *Circadian variation in plasma 17-OHCS*: The circadian pattern is determined by measuring the plasma 17-OHCS at 8 a.m., noon, 4 p.m. and 10 p.m. The normal response is a progressive decrease in the plasma 17-OHCS values from 8 a.m. to 10 p.m. Starting about 4 a.m. the 17-OHCS values begin to rise, reach a peak about 8 a.m., and then start the daily decline. This circadian pattern may be significantly disrupted in hypothalamic disease. It may also be disrupted in temporal lobe, limbic system, and pituitary disease.

**The pituitary-chiasmatic syndrome** consists of a combination of hypo- or hyperpituitarism and visual field defects. This combination is the result of the juxtaposition of the chiasm and pituitary gland rather than a causal relationship between the two structures. Most commonly the syndrome arises in the course of a neoplasm of the pituitary. Occasionally it may arise from any other type of mass in this area, *e.g.*, meningioma, aneurysm, metastasis, chordoma. At times there is a concomitant parasellar syndrome. That is, the structures lying just lateral to the sella may be affected, giving rise to oculomotor palsies or temporal lobe seizures.

The most common type of visual field defect in this syndrome is a bitemporal hemianopia. At times this may involve only the central fields rather than the peripheral vision. The bedside techniques useful for demonstrating such defects are described in another section of this monograph.

The various endocrine manifestations will be discussed below, under disorders of the anterior pituitary gland.

The clinical evaluation of patients with this syndrome should include visual

fields, lumbar puncture, pneumoencephalography, arteriography, electroencephalography, and an endocrine evaluation (Table I).

**Endocrine disorders with central nervous system manifestations** comprise a large group which will here be described in outline:

### **Anterior pituitary**

**CNS Manifestations:** *In course of Neoplasm:* bitemporal visual field defects, seizures, oculomotor palsies, headaches. *In Acromegaly:* headaches, root pains, plus above. *In Cushing's Syndrome:* confusion, psychosis; occasionally associated hyperpigmentation and signs of pituitary neoplasm. *In Simmond's Disease:* psychosis, generalized weakness, emaciation. *In Sheehan's syndrome:* chronic, panhypopituitarism; acute, may have vasomotor collapse. *In Anorexia nervosa:* no signs of CNS disease. Symptoms of hypothyroidism and hypoadrenocorticism may appear in pituitary hypofunction due to any cause.

**Tests:** Visual fields, lumbar puncture, angiography, pneumoencephalography, EEG. Endocrine, see Table I.

### **Posterior pituitary**

**CNS Manifestations:** In case of hypofunction, if severe, dehydration with confusion; diabetes insipidus may occur as part of head trauma syndrome.

**Tests:** Urine specific gravity, effects of antidiuretic hormone, Hickey-Hare test.

*Inappropriate secretion of antidiuretic hormone (ADH)* may occur in a number of central nervous system and possibly even in peripheral nervous system disorders. This syndrome is characterized by evidence of disease of the nervous system (most commonly diffuse cerebral dysfunction varying from a mild organic mental syndrome to coma). At the same time there is water intoxication associated with hyponatremia. Along with the hyponatremia, there is hypertonic urine. Hypertonic saline infusions aggravate the condition. Water restriction alleviates the symptoms. This syndrome may represent posterior pituitary hyperfunction. The appropriate laboratory tests are: determinations of serum sodium, serum osmolality, urine osmolality, and urinary sodium. To establish the diagnosis it is also necessary to eliminate renal and adrenal disease as the cause of abnormal salt and water metabolism.

### **Adrenal cortex**

**CNS Manifestations:** *In course of Cushing's syndrome:* psychosis. *In course of Addison's syndrome:* irritability, occasional seizures (hypoglycemia). *In course of Waterhouse-Friedrickson's syndrome (Meningococcemia)* acute adrenal cortical failure. *In course of Aldosteronism* (excessive production of aldosterone): hypertension, intermittent cramps and muscle pains, weakness, tetany, paralysis, polyuria. *Aldosterone excretion* may be dis-

turbed, particularly in the face of dietary salt restriction, in cases of tumors in the region of the pineal gland.

**Tests:** Low serum potassium, moderately elevated serum sodium, alkalosis, elevated urinary aldosterone, EKG-changes of low potassium.

### **Adrenal medulla**

**CNS Manifestations:** In course of medullary hyperfunction: periodic headaches, anxiety state, seizures, vertigo, paroxysmal hypertension, signs of cerebral hemorrhage.

**Tests:** Vanillyl mandelic acid (VMA) and catecholamines (urinary). Latter may be high in myasthenia gravis and muscular dystrophy. VMA may be increased where catecholamines are normal. VMA may be elevated in neuroblastoma.

### **Pancreas**

**Hypofunction—CNS Manifestations:** In course of *Diabetes*: peripheral neuropathy, myelopathy and encephalopathy.

**Hyperfunction—CNS Manifestations:** Confusion, seizures, coma in course of hypoglycemia, paroxysmal anxiety, automatism.

**Tests:** Glucose tolerance (5 hour), preferable at same time as EEG. Tolerantamide test.

### **Thyroid\***

**Hypofunction—CNS Manifestations:** *Cretinism*: retarded development, especially mental. *Myxedema*: bradyphrenia, confusion, lethargy or agitation or psychosis, diffuse weakness, coma, hypothermia, *Myotonia* may accompany myxedema.

**Tests:** See Table 1. If in hypothyroidism thyroid stimulating hormone (*TSH*) is elevated, the disease is primary to the thyroid. If *TSH* is low, the disease is of pituitary origin.

**Hyperfunction—CNS Manifestations:** Tremors of digits, hyperkinesis, excitement, exophthalmos, exophthalmic ophthalmoplegia, convergence weakness; muscle weakness (especially anterior thigh) and cramps, myasthenia gravis, myopathy which if acute may be bulbar in type; periodic paralysis may occur.

\* Organic iodine compounds used in neuroradiologic contrast studies interfere with protein-bound iodine (PBI) determination. Hypaque and Diodrast interference lasts 3 to 7 days; Pantopaque and Lipidol for 6 months to 5 years. These products also affect the radioactive iodine uptake (RAI). Dilantin may induce a spuriously low PBI without hypothyroidism since Dilantin combines with thyroid binding globulin and interferes with its acceptance of thyroxin. This creates a situation wherein the PBI is low, the  $T_3$  uptake is high, and the patient is euthyroid. When a contrast medium such as Hypaque or Pantopaque has been used, the  $T_3$  resin test can be used.

If a radioactive iodine brain scan is contemplated, the thyroid must be evaluated prior to introduction of the radioactive iodine.

**Tests:** *PBI, BMR, LATS* (Long acting thyroid stimulating hormone) increased in exophthalmos. *TSII* normal except in Grave's Disease due to pituitary neoplasia and in hyperthyroidism associated with acromegaly.

### **Parathyroid**

**Hypofunction—CNS Manifestations:** Carpopedal spasm, convulsions, head retraction, neck pain, muscle cramps, Chvostek's sign.

**Tests:** See Table 1.

**Hyperfunction—CNS Manifestations:** Diffuse weakness, mental depression.

**Tests:** See Table 1.

**Pseudohypoparathyroidism—CNS Manifestations:** Mental deficiency, tetanic convulsion, seizures; calcification of basal ganglia in person of short stature, round facies with a short digit or two, thick skull and cataracts.

# The Lumbar Puncture

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The standard neurology textbooks describe the technique for lumbar puncture and discuss the meaning of the results. This section presents the experience at The Mount Sinai Hospital particularly where it differs from the classical view.

The initial cerebrospinal fluid (CSF) pressure is obtained while the patient is lying in a lateral position with the head in neutral, flexion, and extension positions. An initial pressure of over 200 millimeters of fluid is indicative of intracranial pressure, but there are many patients with ophthalmological evidence of papilledema in whom the increased intracranial pressure is not reflected in the manometric reading. Patients with large mass lesions diagnosed by angiography with major shifts of the anterior cerebral arteries have been found to have normal manometrics. In our experience, comparing the final to initial CSF pressures (Ayala index) is not an accurate indicator of the amount of residual CSF and therefore such readings are no longer taken. Three to five centimeters of CSF is collected and the fluid is processed for cells and protein and, as indicated, for sugar, culture, viral, or immunological studies. Serologic tests of the CSF are of value in determining syphilis of the central nervous system but, for the most part, blood serology tests are of greater value in routine testing for syphilis.

## Indications

Lumbar puncture is a valuable diagnostic test and should be performed in every neurological problem. There are no neurological contraindications.

Cushing stated that a lumbar puncture can be dangerous.

One characteristic of the brain under pressure is the tendency to herniate through a cranial defect, and as there is normally an opening at the foramen magnum, a certain degree of protrusion is usually present there. In the presence of such conditions the withdrawal of cerebrospinal fluid from the spinal meninges by a lumbar puncture is often hazardous and it may tend to a sudden wedging of the bulb in the opening, with anemia and paralysis in the vital centers.

Cushing's concept has persisted in many institutions but experience at this hospital has been contrary to his dictum. Although hundreds of such taps have been performed without apparent harm, 87 patients with papilledema who had lumbar puncture were studied. In no instance was a patient with a space occupying lesion harmed by the lumbar puncture. The value of this test was noted in the 18 patients with "non-operative" conditions in which the CSF findings assisted in diagnosis and management. Twelve of these patients suffered from pseudopapilledema, serous meningitis, lead poisoning, torulosis, or

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subarachnoid hemorrhage. The remaining six were discharged undiagnosed after angiography and/or pneumoencephalography revealed no demonstrable pathology. The lumbar puncture is now performed in all such patients especially since the alternative procedure, the ventricular tap, has hazards greater than those of lumbar puncture.

The only contraindication to lumbar puncture is the presence of infection of tissues at the site of entry. Occasionally direct entry into the spinal canal is blocked by bony abnormalities. An oblique approach from  $1\frac{1}{2}$  to 2 inches lateral is often successful in such instances. Cisternal puncture (in the high cervical region) is the alternative.

### **Diagnostic Value of the Lumbar Puncture**

In all cases in which the localization of pathology is in the spinal canal a Queckenstedt test is performed with the head in three positions, that is, mid-position, acute flexion, and hyperextension. Occasionally when a spinal subarachnoid block exists only a few drops or no spinal fluid at all is obtained. In such cases several cubic centimeters of pantopaque should be injected into the space for outline of the lesion on subsequent x-ray. It is important to have pantopaque on hand since it is thought that after an initial lumbar puncture there is increased likelihood of a subdural injection. A series of four hundred cases were reviewed at this hospital in an attempt to clarify this problem. There were however too many factors which could not be evaluated. Invariably most of the neurological patients presented diagnostic problems and the spinal fluid information prior to pantopaque myelography was an essential part of the diagnostic work-up. On the other hand on the neurosurgical service patients predominately suffered from relatively typical cases of lumbar sacral radiculopathy. The etiology was assumed to be due to herniated intervertebral discs and therefore the analysis of the spinal fluid was not considered essential. There were also patients who had no previous lumbar puncture but on initial puncture pantopaque nevertheless was inadvertently placed subdurally or epidurally. In spite of inconclusive evidence it seems to be preferable to do a diagnostic lumbar puncture prior to injecting pantopaque for contrast study—except in the occasional clear cut diagnostic entity.

### **Abnormal CSF Findings**

**Color.** Comparison with a similar tube of water against a white background is the criterion generally used for deciding if cerebrospinal fluid is "clear and colorless." Although with intracranial hemorrhage the spinal fluid is usually bloody or xanthochromic, at times it is clear for the first 24 to 48 hours of the illness. When a traumatic tap is suspected the fluid is collected in four tubes and compared as to the degree of blood in each. One tube may be centrifuged and the supernatant examined. Also a drop or two of fluid may be placed on a white cloth (towel or sheet) and the stain observed as it spreads. If the tap is traumatic a red ring will remain toward the center while a clear ring spreads out. Subdural hematomas usually give xanthochromic fluid but in many instances

the fluid has been normal. In jaundiced patients the fluid may be xanthochromic due to bilirubin. However since in many cases it is often colorless such patients should be investigated for other causes of xanthochromia.

**Cells.** Increase in lymphocytes above 5 to 10 per cubic mm is abnormal. This indicates an inflammation either bacterial, viral or aseptic, or a neoplastic process—especially blood dyscrasias. Pneumoencephalography is frequently followed by a pleocytosis and at times quite intense cellular reactions have been seen. Rarely malignant cells with mitosis have been found and, uncommonly, a large abnormal polymorphonuclear cell has been reported which has correlated with meningocarcinomatosis, chronic inflammation of the brain, and chronic obstruction due to Arnold-Chiari deformity.

**Protein.** Elevation of the CSF protein is a frequent finding in diseases of the nervous system. Conditions including infections, Guillain-Barré syndrome and neoplasm all elevate the CSF protein. Diseases which elevate the serum globulin frequently reflect this abnormality in the CSF, e.g., multiple myeloma. The CSF gamma globulin has also been found elevated in multiple sclerosis in the presence of normal serum proteins. It is frequently stated that CSF protein is elevated in diabetic patients with spinal cord, root and/or nerve disease. In a series of 192 patients suffering from myeloradiculopathies (not peripheral neuropathies), of 51 patients who had laboratory evidence of diabetes mellitus, 28 had normal cerebrospinal fluid. The twenty-three remaining patients had abnormally elevated CSF levels but at least 15 of these had obvious causes other than diabetes for the elevated CSF protein. Of the 141 patients without evidence of diabetes 61 had elevated CSF protein. In 36 of the 61 there was obstruction of or impingement upon the spinal canal. In 13 of the 61 there was no explanation for the abnormal CSF findings. The analysis of this data did not support the conclusion that the findings of elevated CSF protein in a patient with myeloradiculopathy should suggest the presence of diabetes. Moreover: even when the complete triad is present (myeloradiculopathy, diabetes, elevated protein), diabetes does not necessarily underlie the others. Such a patient is more likely to have mechanical encroachment upon the spinal canal.

### **Therapeutic Value of Lumbar Puncture**

At times the intrathecal route for administration of antibiotics is employed in certain infections, e.g., tuberculosis, torulosis. Recently steroids have similarly been given in patients with acute multiple sclerosis and generalized polyradiculopathy, but the results are inconclusive and still in the experimental stage. However, in our experience we have noted that the use of 40 mg of Depo-Medrol has been quite efficacious in diminishing the reaction of pneumoencephalography, pantopaque myelography, and even the lumbar puncture itself. We have at times performed repeated lumbar punctures with apparent good results in patients with increased intracranial hypertension of an unknown cause. In some cases of intractable pain due to chronic irritation of lower spinal roots without evidence of intraspinal pathology intrathecal injections of Depo-

Medrol may be of value. It is especially valuable in cases of pain with so called "herniated disc" without manifest protrusion.

### **Complications**

The lumbar puncture is almost always a harmless procedure. A nerve root may be traumatized upon entry of the needle which causes transient pain down the under surface of the leg. The most common sequel to lumbar puncture is headache which develops during the first twenty-four hours after the procedure and may last a week or even longer. Lying flat in bed after procedure may diminish or prevent this and, as mentioned above, an injection of Depo-Medrol reduces this sequela.

# Contemporary Electroencephalography An Empirical Approach

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## What Can the EEG Do?

Many people have illusions about what electroencephalography can do. Perhaps because so few physicians have direct experience with it, so many have distorted ideas of its utility. A frequent statement on institutional request forms is: "rule out organic disease," or "rule out epilepsy." Obviously, what is often expected in an EEG report is a diagnosis; a specific answer with specific prognostic and therapeutic implications.

This expectation is rarely, if ever, realized. The EEG is only one of many sources of data *for clinical* management and diagnosis; a certain level of experience and understanding is necessary for its proper and efficient use. Like newer techniques such as radioactive isotope brain scanning and sonoencephalography, the EEG has value in that it is a relatively simple and painless *technique and adds* another dimension to the data which are integrated by the neurologist in his assessment of a case. This technique makes possible the perception of the spontaneous electrical activity of the brain. The EEG *monitors* one band of the *broad* spectrum of electrical events taking place in the brain; this band being determined by the nature and placement of the electrodes and the characteristics of the amplifying and recording devices. Highly localized cortical neuronal and dendritic potentials and massive cortical DC shifts are equally unavailable to most standard recording equipment. Both normal and abnormal activity of many types may occur in the depths of the brain and not be manifested by changes in potential at scalp electrodes. In spite of these limitations, valuable information about the electrical aspects of brain function can be recorded in the EEG, and this electrical activity has been shown to stand in an orderly relationship to other aspects of brain function.

## Defining the Normal EEG

Over the years, a group of patterns associated with "normal" brain function have come to be recognized, i.e. tracings seen in persons without demonstrable brain lesions or organic dysfunction as determined by clinical criteria. At the same time, we have built up an empirical classification of "abnormal" records.

From the Department of Neurology and Electroencephalography Laboratory, The Mount Sinai Hospital, New York, N.Y. Supported by U.S.P.H.S. Grant NB—05221.

Electrode placements calculated according to the 10-20 International System. Designations as follows: F (frontal); C (central); P (parietal); O (occipital); AT (anterior temporal); MT (midtemporal); PT (posterior temporal); E (ear-lobe or tragus); V (vertex, midcentral).

In general, certain types of patterns correlate with other indices of organic cerebral dysfunction to a very high degree of probability.

It has often been stated that "abnormal EEGs" could be seen in as much as 15 per cent of the "normal population." There is an inherent contradiction in such a statement which implies that either the population is not truly "normal," or that the EEG criteria were chosen arbitrarily rather than empirically. Indeed there may be an abnormality which manifests itself only by changes in the EEG. However, when we speak in terms of clinical electroencephalography, our criteria for abnormality must be susceptible to clinical verification.

Thus we should limit "abnormality" in the EEG to those cases where there is definite organic brain disease or dysfunction. EEGs reported as abnormal in the absence of gross clinical evidence of brain dysfunction should, thus, in almost all cases be due to prior, unrecognized, or latent disease.

**The recording system.** The EEG represents the continuously fluctuating potential difference between two points on the head. The electrodes are placed according to a standardized method with the electrode-pairs usually linked in such a way as to give comparable tracings from homologous regions on the two sides. Sometimes the individual electrodes are paired with a single common reference point or arranged in longitudinal or transverse linear montages. The equipment used gives fairly faithful recording of frequencies from 1 to 40 cycles per second and amplitudes from 5 to 500 microvolts. The tracing is written out by a moving stylus calibrated to a vertical excursion of 5 to 7 mm for each 50 microvolts of input on a horizontally continuous strip of paper which advances at a speed of 3 cm per second. Most of the equipment now in use writes eight such traces simultaneously but devices with twelve, sixteen, or more channels are available.

**Normal waveforms.** Using this equipment, the EEG of the normal alert adult consists almost entirely of fairly symmetrical activity in the alpha (8 to 13 cps) and beta (14 to 30 cps) bands with the alpha activity predominating over the posterior portions of the head and the beta activity predominating over the anterior portions (Fig. 1). There is an extremely wide range of normal variation in the voltage and in the absolute and relative amount (per cent time) of these rhythms. A series of striking changes takes place in the tracing as the patient becomes drowsy and goes to sleep; the slower theta (5 to 7 cps) and delta (less than 4 cps) waves appear irregularly and paroxysmally. There are also certain characteristic patterns of normal sleep such as "sleep spindles" and "vertex sharp waves."

**Infancy and childhood.** The EEG of the infant and child is much more difficult to analyze and interpret. A certain amount of slow activity is normal in children—very low frequencies are acceptable as within normal range in very young children. A variable amount of asymmetry may be encountered in normal children. Unrecognized drowsiness or involuntary hyperventilation may affect the EEG record by introducing slower potentials or paroxysmal discharges. The greater difficulty encountered in obtaining technically satisfactory



tracings is also a factor which contributes to the problem of unreliability in the interpretation of the EEG in the child.

**Artifacts.** The competent electroencephalographer must start with the ability to distinguish activity in the tracing which is of cerebral origin from that which is due to any of a number of other factors: movement of the head or eyes, movement of the extremities, facial muscle contraction, perspiration, faulty electrodes, defects within the apparatus, and broadcast activity from electrical equipment in the vicinity. This distinction is always an important but not a simple one. Having determined that the activity derives from the brain, the electroencephalographer must take into account the age and level of conscious-

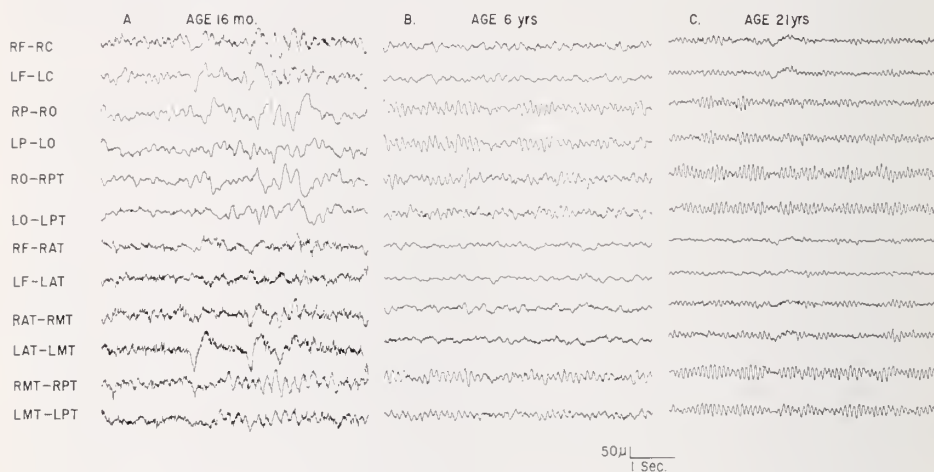


FIG. 1. Evolution of the basic patterns in the normal, alert individual. Slow patterns predominate in infancy, persist in the presence of the alpha rhythm in childhood, and are absent in the adult.

ness of the patient. When this is done he may begin to speak in terms of "abnormality" or dysfunction.

**Abnormal activity.** In general, the most common evidence of dysfunction is activity which is of a frequency lower than that consistent with the patient's age and level of consciousness. This *slowing* may be either generalized or localized. Consistent asymmetry of the frequencies is abnormal; the slower side is usually the abnormal one. Localized absence of activity, and highly localized sources of high-frequency activity are much less common types of abnormality. Diffuse absence of activity is a rare abnormality signifying either temporary or permanent loss of cerebral function.

Spikes and polyphasic complexes containing *spikes* or *sharp waves* are abnormal whenever seen regardless of age or level of consciousness. They occur in transient patterns which tend to be morphologically stereotyped and which stand out from the background activity in such a way as to be readily recognizable.

## Specific Uses of the EEG

### As a Screening Procedure

Some patient's complaints are so vague and non-specific as to raise the question of whether the nervous system is involved at all. The EEG may be used as a screening procedure in such cases. A patient with an isolated complaint of severe headaches, lethargy, or subtle personality changes may show localized or diffuse EEG abnormalities. A patient with ill-defined weak spells, episodic vertigo, or fainting may have EEG abnormalities indicating the likelihood of a convulsive disorder.

It must be emphasized that a "negative" or normal EEG does not "rule out" organic brain disease or dysfunction in such cases but is only one factor in the total evaluation of the case. For example, in cases of episodic phenomena where convulsive disorder is strongly suspected, it may be that only by using special techniques such as photic stimulation or sleep recording that characteristic abnormalities are elicited. It is also perfectly possible that organic disease or dysfunction may be present but simply not manifest in the EEG.

Although the percentage yield of "positive" EEGs may be small in cases such as those described above the relative ease and innocuous nature of the procedure makes it worthwhile for screening purposes.

### With Specific Clinical Conditions

Very often the EEG is of great value in contributing to the understanding of the localization and even the etiology of the lesion or dysfunction responsible for a specific clinical syndrome. There may be a focal lesion, such as a right frontal meningioma, which produces only mental changes, without focal neurologic signs and yet shows a marked slow-wave focus on the EEG. Lateralization of the lesion may also be determined by the EEG in cases in which marked diffuse clinical signs mask the focal ones such as spontaneous subarachnoid hemorrhage due to ruptured aneurysm.

Valuable information may even be obtained from apparently wrong sided or "paradoxical" foci of electrical dysfunction. When a clear-cut focal EEG abnormality exists on the side opposite to the one expected on clinical grounds, it almost invariably signifies the presence of either multiple lesions or incorrect clinical localization.

**Etiology.** The EEG is a far less reliable indicator of the nature of the focal lesion suggested by the localized electrical dysfunction. In general, more pathologically "active" (rapidly growing, destructive) lesions tend to produce more marked focal slowing, and more benign or slowly evolving lesions tend to produce less evidence of electrical abnormality. There are many exceptions to this generalization, however, and even the conforming examples are of little practical value. A severe slow focus may with equal likelihood be due to a glioblastoma, an abscess, or an intracerebral hematoma.

**Seizure states.** The EEG is of much greater value in defining etiology (or pathophysiology) in seizure patients. Patients with both major and minor

convulsions may show identical, unlocalized seizure phenomena whether they have dysfunctional ("centrencephalic") convulsive disorder or focal epileptogenic lesions. It is only the EEG which enables the distinction to be made, and this is a very important distinction, since it is of great help in guiding the medical management of the case, or suggesting that surgical treatment may be possible.

**Coma.** The underlying pathophysiology may also be indicated by the EEG in cases of apparent coma. Ordinarily, comatose patients show abnormal EEGs characterized by diffuse irregular slow activity. Many patients with severe metabolic abnormalities, however, such as those seen in hepatic insufficiency and severe uremia, show a fairly characteristic pattern of repetitive, bisynchronous, polyphasic sharp complexes accentuated over the anterior scalp. Patients who appear to be in coma following severe transverse lesions of the lower brainstem may show perfectly normal tracings, and patients in deep barbiturate coma may have EEGs resembling normal light sleep with some "medication effect."

**Behavior disorders.** Another area in which the EEG is helpful in defining the clinical problem is that of grossly disordered behavior in both adults and children. Periods of mental dullness, restlessness, or confusion lasting as long as two or three days may actually be prolonged seizures ("dreamy states," "ictal automatisms," "psychomotor status"). An EEG during the episode enables the diagnosis to be made immediately (Fig. 2). An abnormal EEG containing spikes or spike-wave patterns, if obtained between the episodes of confusion, suggests that the episodes are ictal in nature.

Many children are referred for evaluation of retardation or behavior disturbance without a history of frank convulsive phenomena (Fig. 3). A certain proportion of such children will show grossly abnormal EEGs of "convulsive" type. The concept of "subclinical seizures" has been invoked to explain some or all of the behavioral abnormalities in these children. The validity of this concept has been tested, and in some instances proven, by the successful use of anti-convulsant medication. Normalization of restless behavior and improvement in school performance and IQ can occur. Another group of these children will show focal abnormalities in the EEG due to the presence of underlying lesions such as porencephalic cyst, angiomaticus malformation, or microgyria. The disclosure of such a focus may emphasize the need for further neurologic diagnostic studies or more detailed behavioral testing for specific defects such as aphasia.

### **Monitoring the Course of Illness or Treatment**

**Anti-convulsant medication.** For many years the EEG has been used as one index for weighing the efficacy of anti-convulsant medication. In many cases the "normalization" of the EEG follows, or even precedes, clinical improvement. This phenomenon may be used in helping to determine dose levels, choice of medication, and duration of medication following the cessation of seizures. It

is also used as a criterion in the granting of driver's licenses to convulsive disorder patients.

**Metabolic disorders and toxic states.** The EEG is also useful in following and sometimes predicting the course in patients with metabolic disorders (Fig. 4). These include: hypercalcemic encephalopathy and hepatic encephalopathy;

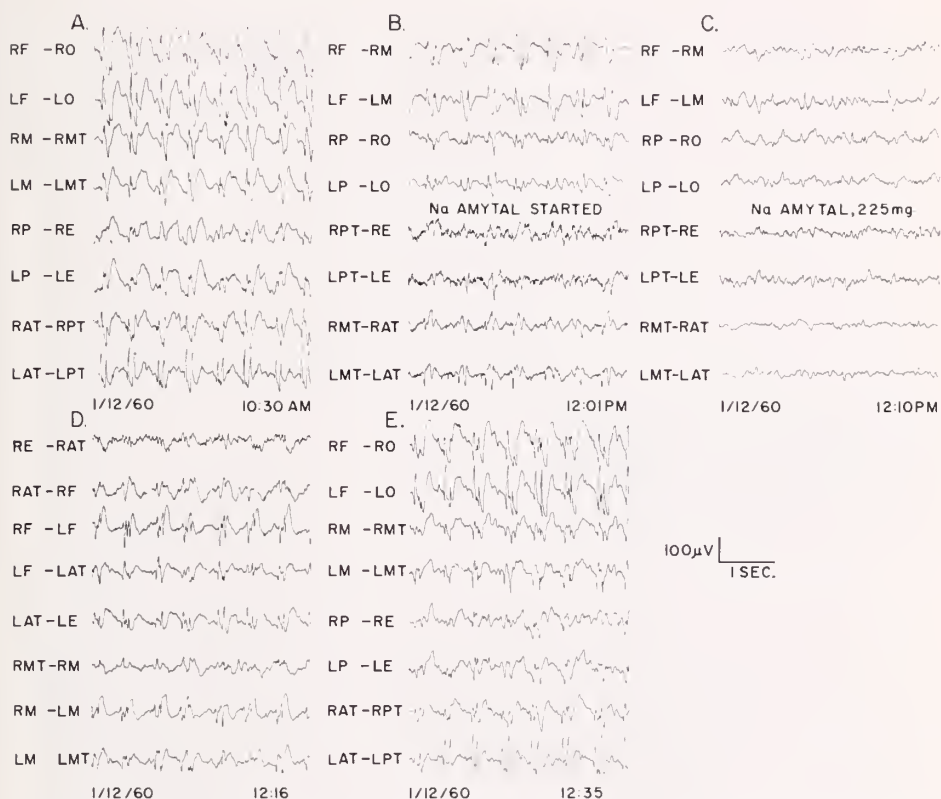


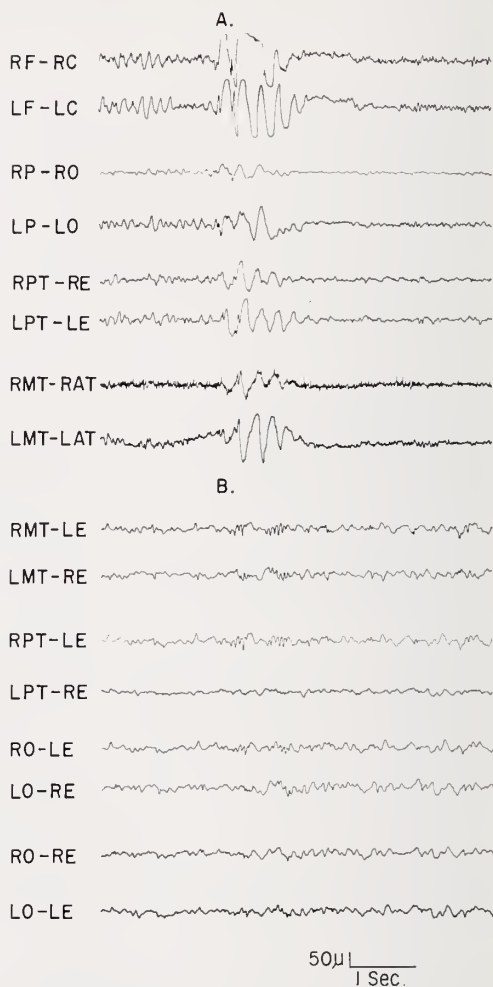
FIG. 2. Tracings performed during an "ictal twilight state" (psychomotor status) lasting thirty-six hours. Transient cessation of spike-wave activity with increase in responsiveness after intravenous amobarbital.

withdrawal from drug intoxication (Fig. 5); and acute or chronic infections such as viral encephalitis and tuberculous meningitis.

**Intracranial mass lesions.** The non-surgical treatment of intracranial mass lesions is another area of usefulness for the EEG. Electrical as well as clinical indices are of value in assessing the efficacy of radiotherapy and/or steroid therapy in primary or metastatic brain tumors. The EEG is also of value in following the clinical course of unoperated subdural hematoma patients (Fig. 6). The EEG may be normal at the start or may become normal in the presence of a hematoma of appreciable size. Most of these patients improve and the EEG

improvement tends to precede or accompany the clinical improvement even though a mass lesion may still be present. In rare cases, an increase in EEG abnormality may precede, or accompany a significant deterioration in the patient's condition, and may be a sign that operation should be considered.

FIG. 3. Eleven year old boy with severe behavior disorder. No history of convulsive phenomena. Tracing shows a spike-wave burst in drowsiness and "14 per second monophasic spike burst" in sleep.



## Treatment and Clinical Research

**Seizure patients.** There are many special procedures which involve the use of the EEG some of which are quite important. Special techniques are particularly employed in dealing with seizure patients. As mentioned before, tracings performed during sleep may reveal a previously undisclosed focal or diffuse abnormality. Intravenous pentobarbital or amobarbital may be used to indicate the presence of localized brain dysfunction. These techniques are particu-



larly important in patients who are being studied for possible surgical treatment. Special electrode placement, such as on the tympanic membrane or in the nasopharynx, may be used. The EEG is used during the intracarotid injection of convulsant and anti-convulsant drugs for confirming cerebral dominance and for proving the limited localization of an epileptogenic focus. Prior to actual exposure of the cortex, arrays of electrodes may be slipped through burr holes to lie be-

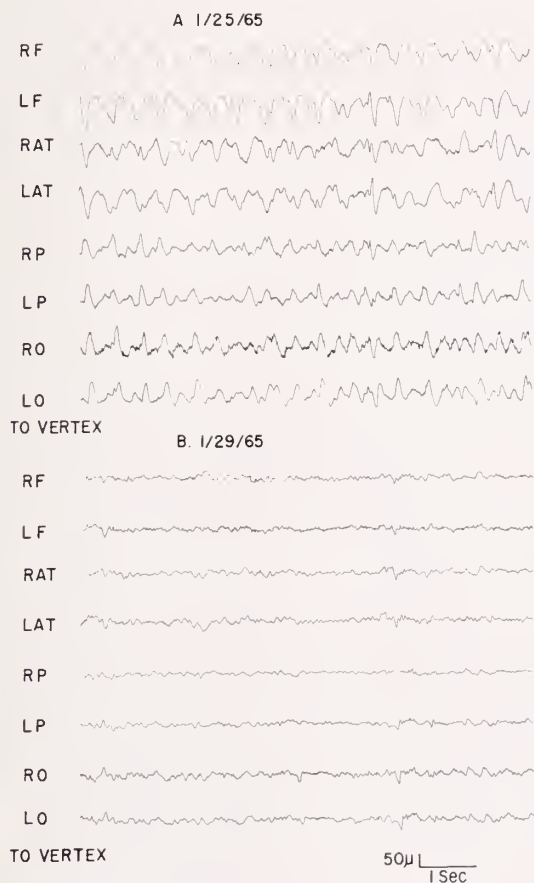


FIG. 4. Patient with portal cirrhosis and hepatic encephalopathy. A. Deep coma. Tracing shows severe diffuse slowing and repetitive polyphasic sharp complexes. B. Alert and responsive. Tracing shows only mild diffuse slowing.

tween the dura and the arachnoid and depth electrodes may be implanted for hours or days of study. During the definitive surgical procedure the EEG is in constant use in locating and mapping the foci of electrical abnormality. This is particularly important in the cases which show no grossly visible pathology.

**Photic stimulation.** Medically treated seizure patients may also benefit from special EEG techniques. For example, there are some individuals, especially children, who have myoclonic jerks, lapses, and even convulsions when exposed to intermittent, or even steady, intense light. Testing such patients with lights of varying intensities and with filters for different colors may not only

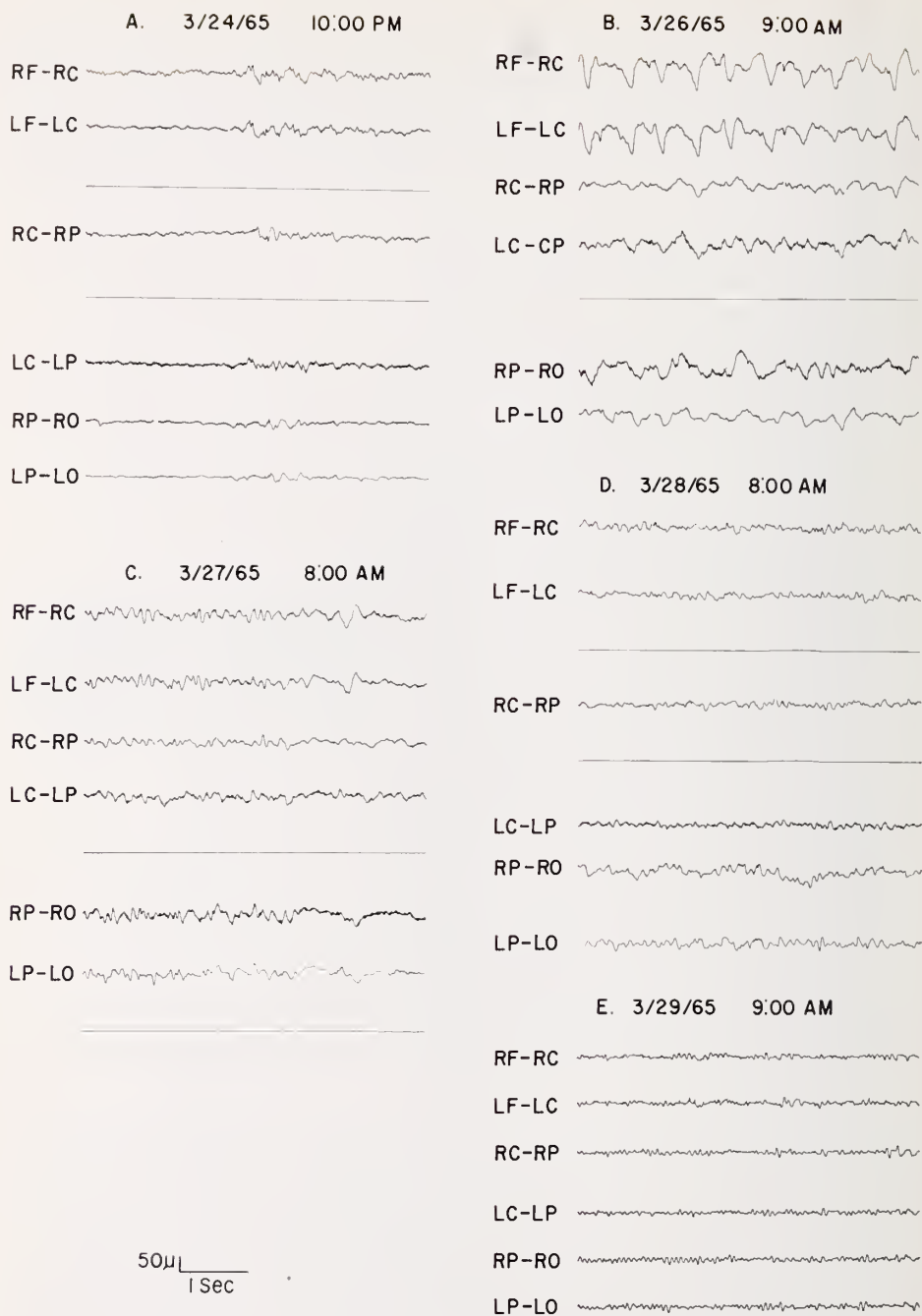


FIG. 5.

explain the often bizarre and unusual circumstances under which the seizures have occurred, but may yield a formula for dark glasses which will protect the patient against seizures.

**Anti-convulsant drugs.** EEG monitoring during the intravenous injection of anti-convulsant drugs in a patient with a high per cent time of abnormal activity, or who is in status epilepticus, may help to predict which drug is likely to be effective when given orally.

**Carotid sinus hypersensitivity.** The EEG and the electrocardiogram may be monitored simultaneously when a patient is being tested for carotid sinus hypersensitivity. This technique should also be followed when the carotid compression test is being done. As one carotid artery is manually compressed, the

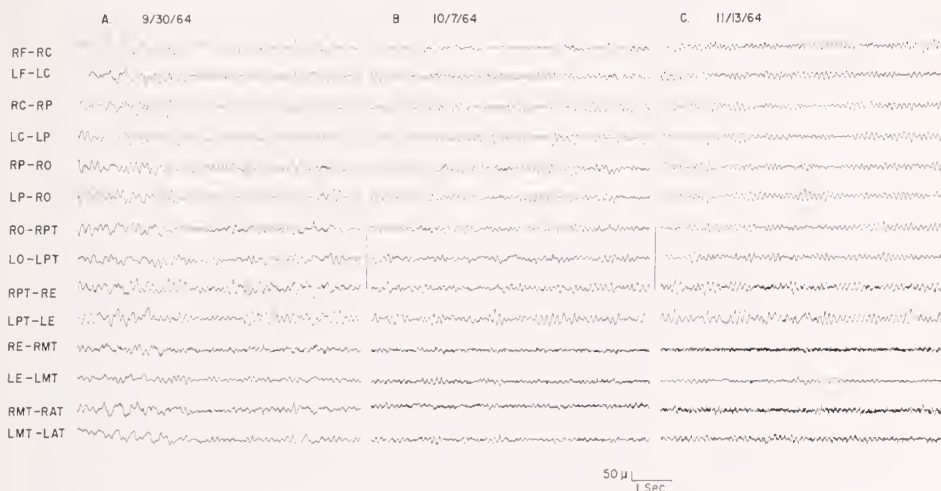


Fig. 6. Serial tracings show progressive improvement in a 68 year old man with a spontaneously improving left sided subdural hematoma.

patient is observed for the development of loss of consciousness, focal weakness, or focal seizure phenomena. At the same time the EEG is observed for focal or diffuse changes. Early hopes have not been fulfilled that a "positive" carotid compression test would reliably indicate severe stenosis or occlusion of the opposite carotid artery. The procedure is nevertheless of value in some cases since at the very least it gives some information about the efficacy of the collateral circulation in the circle of Willis.

**During anesthesia.** In recent years the EEG has come to be used in some centers as a tool in monitoring patients under anesthesia, especially for open-

Fig. 5. Patient in severe acute barbiturate intoxication. A. Deep coma, occasional "decerebrate" posturing. Artificial respiration, hemodialysis in operation. Tracing alternating between mixed frequency slow bursts and isoelectric periods. B. Deep coma, unresponsive. Artificial respiration. Tracing shows marked diffuse slowing with polyphasic sharp complexes. C. Coma, occasional spontaneous movements of eyes and extremities. Tracing alternates between 8 to 10 cps activity and relatively "flat" periods with some slowing. D. Awake, lethargic. Tracing shows diffuse 7 to 15 cps activity. E. Completely alert and cooperative. 13 per second alpha rhythm with low voltage fast activity.

heart surgery. An orderly progression of EEG changes has been found, with correlations to the depth of anesthesia as indicated by other measures. In some instances this can be of great value to the operating surgeon. The maintenance of satisfactory EEG patterns can be the most reliable index of proper function-

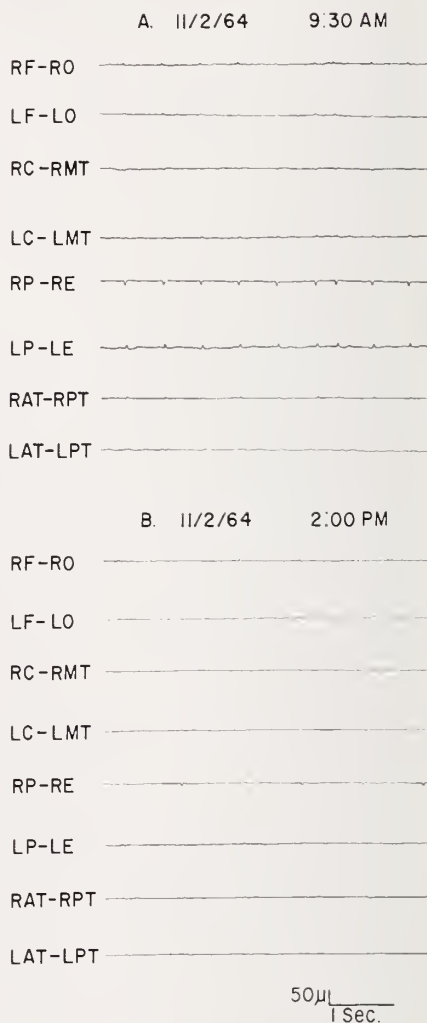


FIG. 7. EEG tracings in a patient four days following operation for anterior communicating artery aneurysm. No evidence of cerebral activity during a five hour period. Tracing completely flat except for EKG artifact.

ing of an extracorporeal circulation apparatus. The appearance of diffuse flattening of the tracing serves as a warning that only a very brief period remains during which circulation to the brain must be restored or else permanent damage, or even death, may result.

This phenomenon (the appearance of a flat EEG) has been proposed for use as one criterion in determining when "death" has occurred in a patient who is being maintained on artificial respiration and/or external cardiac pacemaker

stimulation (Fig. 7). This problem is certain to increase in its prevalence as more people undergo reconstructive surgery on vital organs, and some day precise and universally acceptable standards of definition may be determined.

**In psychiatry.** As a result of the obvious attractiveness of the idea of a possible objective electrical correlate of thought processes, there have been, over the years, many attempts to use the EEG in psychiatric practice and research. In general, these attempts have been unsuccessful, although many papers have presented correlations of EEG abnormalities and various psychiatric diagnoses. Statistical methods have had to be invoked to support these relationships, and there is much difficulty involved in agreeing on both psychiatric and EEG diagnoses. A current example of the use of EEG in clinical psychiatry is the somewhat controversial correlation of certain personality characteristics with "14 and 6 per second monophasic spikes." This is a pattern which appears primarily in the sleep records of young people and has been linked to behavior characterized by impulsivity, aggressiveness and blunting of affect.

While there is no direct correlation of actual thought content (normal or pathologic) with EEG phenomena, routine EEG may be of indirect value in the management of psychotic patients. During initial evaluation the EEG has some validity as a screening procedure. During treatment, particularly electroconvulsive or intensive pharmacologic treatment, the EEG may be of value in confirming or even predicting efficacy. In psychiatric research there has been increasing use of special techniques such as electronic frequency analysis, autocorrelation and cross-correlation, and energy output measurements.

**Sleep and dreaming.** The EEG is also the technical basis for a whole new field of research in the physiology of sleep and dreaming. The simultaneous recording of the EEG, eye movements, and, at times, muscle action potentials is carried on through hours of natural sleep. Various levels of sleep can be identified and there is much evidence to indicate that the periods of active dreaming can also be identified. With this as a tool a great many research studies have been undertaken.

## SUMMARY

Electroencephalography is a laboratory method of great value in the management of patients with nervous system diseases. In some cases it is the only method which can yield reliable, permanent, objective data to establish or define the physiological basis for a clinical diagnosis. In other cases EEG phenomena are useful in conjunction with other laboratory methods. The signal upon which the EEG tracing is based is very complex and dynamic (as opposed to the repetitive stereotyped EKG patterns) and there are many elements of variable but potentially great significance in the equipment, the environment, and the patient's attitude, level of consciousness, metabolism, and state of health. As a result of this complexity the clinical science of electroencephalography *becomes an art*. Although specific definition is usually possible, the actual detection of significant patterns is often based on the direct, non-verbalized, *gestalt* perceptions of the electroencephalographer.



This complexity may also contribute to the variety of diagnostic opinions which can occur among *trained* electroencephalographers in ambiguous or "borderline" cases. In the hands of well-trained, experienced, conservative workers, however, such ambiguous situations should be very rare. Electroencephalography is not only reliable, but also *can be* heuristically valuable and clinically useful.

# Electromyography

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## Introduction

Electromyography is a method of studying the function of various parts of the nervous system by recording the electrical potentials of the muscles and nerves. The abnormal potentials seen in disease states have been observed by many workers so that electromyography can now be used as a diagnostic tool in neurology and can often define in anatomical terms the area of nervous system dysfunction.

The techniques are varied and include the recording of electrical phenomena of muscle tissue at rest, during voluntary activity, and during electrical or mechanical stimulation of nearby nerves. These various techniques to be described are complimentary and are usually of most help when done in combination on the same patient.

## The Neuromuscular System

The most common question posed by the clinician to the electromyographer is: "What is the anatomical location of the patient's weakness?" For the purposes of electromyography the neuromuscular system is divided into four anatomical categories. The neurogenic disorders include: 1) the *upper motor neuron*, which includes all neurons which control or influence the lower motor neurons of the spinal cord or brainstem; 2) the *lower motor neuron* which includes the anterior horn cell and its axon. The myopathic disorders include: 3) the *neuromuscular junction*; and 4) *muscle tissue*.

These anatomical categories are the basis of electromyographic reporting. The etiology of neurologic diseases can frequently be established with greater certainty when the anatomy is known. Because of the nature of these tests, negative results rarely rule out any disease state. Only positive results with definite abnormalities have any clinical meaning.

## The Motor Unit

The keystone of neuromuscular activity is the motor unit. This entity is defined as the total number of muscle fibers innervated by one anterior horn cell. The number of muscle fibers in each motor unit in normal patients varies between 3 and 6 fibers in the extraocular muscles to 1000 to 2000 fibers per motor unit in the larger muscles of the legs. The motor unit is controlled by a single anterior horn cell. The normal motor unit can be observed and defined by projecting the electrical phenomena recorded from the muscle during voluntary effort onto a cathode-ray oscilloscope. The usual ranges of the various motor unit parameters are shown in Figure 1. A large portion of electromyograph in-

The Mount Sinai Hospital, New York, N.Y. Supported by U.S.P.H.S. Grant NB-05221.

terpretation depends on the analysis made of the various motor units during voluntary effort.

**Spontaneous Muscle Potentials.** Recording of muscle potentials can be done either with surface plate electrodes pasted onto the skin, or with a coaxial needle electrode inserted into the muscle. The muscle cells maintain a difference in electrical potential of 60 to 90 mv between the inside and the outside of the muscle membrane. The depolarization of the membrane during voluntary effort occurs immediately before the muscle contraction. The recordings made in electromyography are usually limited to the electrical potential changes and exclude the mechanical movements of the muscle. With suitable amplifying system, the electrical potentials recorded can be seen on a cathode-ray oscilloscope and can be heard on an audio system. Permanent records can be made by means of tape recorders or photographic cameras. The paste electrodes on the skin tend to give a picture of total activity of large parts of the muscle whereas coaxial needle electrodes give greater amount of information regarding a

#### MOTOR UNIT



VOLTAGE	.2 - 5 mv.
DURATION	2 - 8 msec.
FORM	diphasic, triphasic, or polyphasic
FREQUENCY	1 - 20/sec. (depending on effort)

FIG. 1. A. Diagram of the electromyographic response (form) of a typical motor unit. B. The dimensions of the electromyographic response of a typical motor unit. (From: Brock, S. and Krieger, H.: *The Basis of Clinical Neurology*. Baltimore: The Williams & Wilkins Company, 1963.)

smaller portion of the muscle tissue. Both recording methods are useful and will be described with each individual test.

When the muscle tissue is studied, a coaxial needle is inserted into the muscle mass and recording made of electrical phenomena found in the muscle at rest and during voluntary effort. In the normal state there is no electrical activity at rest. In the pathological state abnormal potentials such as fibrillations, positive waves, myotonic phenomena, and fasciculations may be seen (Fig. 2). These phenomena will be described and defined in the next section dealing with disease states. The motor units are then observed during voluntary movement with minimal and then maximal effort. Most muscles of the body can be studied and this includes the limb muscles and muscles of tongue, face, masseter and extraocular muscles. The parameters of motor units are somewhat different in each muscle and therefore observations must be made in relation to the normal values in each individual muscle. The parameters in the extraocular muscles are quite different from the large muscles of the legs, probably because each individual motor unit has a different number of muscle fibers.

**Conduction Velocity.** At the time of recording the muscle potentials, it is frequently of value to stimulate mixed nerves with electrical currents and record electrical activity in the muscle. When the motor nerves are stimulated

the muscle innervated by that nerve will depolarize almost completely in a short period of time. This depolarization can be measured on a cathode-ray oscilloscope and gives us a convenient method to determine the conduction

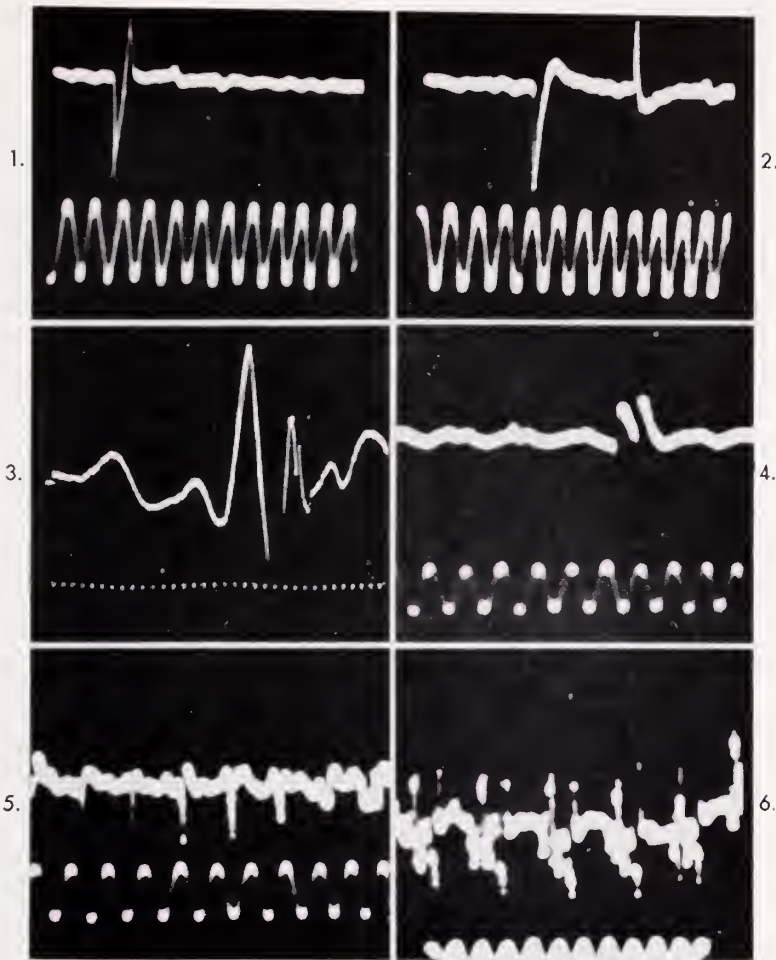


FIG. 2. The Form of the Wave on the Oscilloscope in Various Muscle States. In a normal relaxed muscle, a coaxial needle inserted into the muscle will record no electrical activity. In pathological states various electrical phenomena can be seen. 1. Fibrillation, 1000 cycles/sec. = 0.05 mv; 2. Positive waves, 1000 cycles/sec. = 0.05 mv; 3. Fasciculation, 1000 cycles/sec. = 1.0 mv; 4. Doublets, 100 cycles/sec. = 0.05 mv; 5. Myotonia, 100 cycles/sec. = 0.10 mv; and 6. Bizarre high frequency potentials, 100 cycles/sec. = 0.10 mv. (From: Brock, S. and Krieger, H.: *The Basis of Clinical Neurology*. Baltimore: The Williams & Wilkins Company, 1963.)

velocity of the nerve. A nerve muscle system such as the ulnar-hypothenar system is used. The ulnar nerve is stimulated at the wrist, elbow, and axilla. The time between the electrical stimulation and the muscle depolarization can easily be measured on a cathode-ray oscilloscope. The distance between

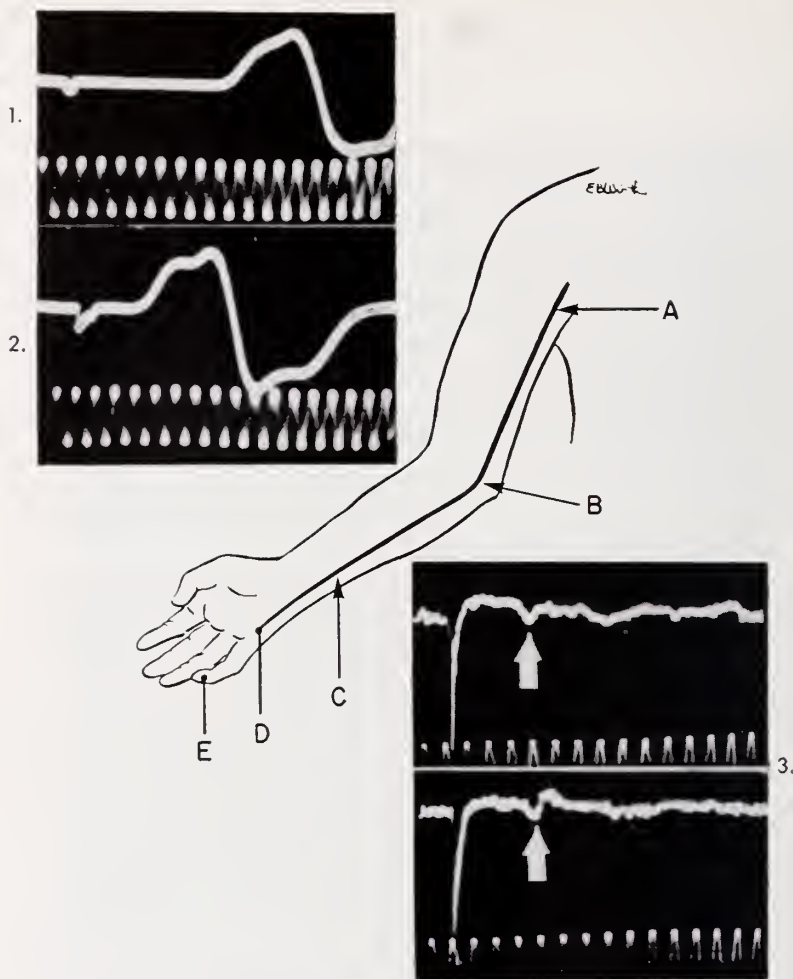


FIG. 3. Stimulation Studies of a Mixed Nerve. The conduction velocity of the fastest motor fiber in a mixed nerve is determined by measuring the time between nerve stimulation and the depolarization of the distal muscle. Two points ( $B-C$ ) of the nerve are stimulated. The distance between these points is measured in centimeters ( $B-C$ ). The time between stimulation of point  $C$  and muscle depolarization (2) is subtracted from time between stimulation of point  $B$  and muscle depolarization (1). This value is divided by the distance ( $B-C$ ). The conduction velocity of segment  $B-C$  is thereby determined. (1) (2) 1000 cycle sine wave = 0.5 mv. The conduction velocity of the sensory fibers of a mixed nerve can be established by stimulation of distal point  $C$  and the recording of the depolarization of the nerve at  $B$  (3). A persistent potential (arrow) is noted approximately 3.7 msec, after the stimulation artifact. The voltage of the nerve depolarization is low with these techniques and multiple stimulations are needed. (3) 1000 cycle sine wave = 0.05 mv. (From: Brock, S. and Krieger, H.: *The Basis of Clinical Neurology*. Baltimore: The Williams & Wilkins Company, 1963.)

points of stimulation can be measured with a tape measure and then the conduction velocity of the segments from axilla to elbow and elbow to wrist can be defined (Fig. 3). In a similar way, sensory nerve fibers can be studied by stimulating the nerves at the finger tips or the wrists and recording made of the



depolarization of the nerve higher in the limb. In addition to these simple studies, complex reflexes can be observed when the nerves are stimulated. The best known reflex is the H reflex. This is an electrical response recorded in the muscle under observation when the mixed nerve is stimulated. The H reflex is a monosynaptic reflex which is mediated in the spinal cord and is in many ways analogous to the deep tendon reflex (Fig. 4).

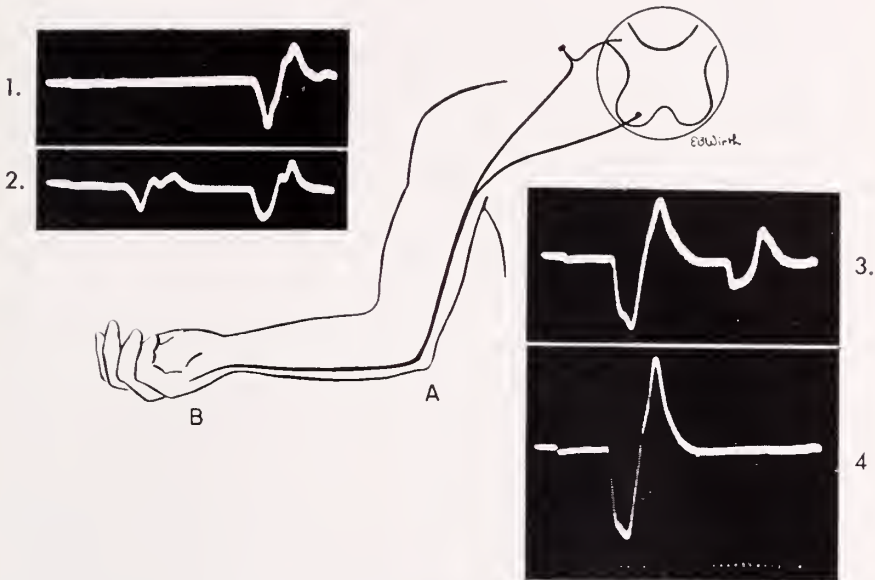


FIG. 4. H-Reflex Studies. In this study the mixed nerve is stimulated at A and the depolarization of the distal muscle is recorded with plate electrodes at B. The nerve is stimulated with increasing voltage (1-3) until supramaximal voltage is reached (4). The initial late response is noted in the submaximal stimulation (1-3). The late response (H-Reflex) is mediated via sensory nerve fiber to the spinal cord and then via motor fibers. With increasing strength the motor fibers are stimulated directly and the early response (M-Wave) is noted in (2-4). The disappearance of the late response during maximum stimulation is probably due to antidromic firing of the motor fiber. 1000 cycle sine wave. (From: Brock, S. and Krieger, H.: *The Basis of Clinical Neurology*. Baltimore: The Williams & Wilkins Company, 1963.)

**Repetitive stimulation.** Repetitive stimulation of motor nerves at rates between 3 and 25 stimulations per second can give information concerning the physiology of the neuromuscular junction. The same system such as the ulnar-hypothener group is used and recordings made of the hypothener muscle during supermaximal stimulation of the ulnar nerve at various frequencies. The response to a single stimulation may be normal but repetitive stimulation may bring out a defect in the neuromuscular junction. This type of testing is of value in the diagnosis of myasthenia gravis.

**Strength-duration curve.** Some of the earliest electrodiagnostic studies used the response of muscles to electrical pulses as a test situation. The most reliable of these many tests deals with the response of the muscle to electrical pulses of varying duration. The minimal amount of voltage needed to cause a muscle

twitch is determined for a series of stimuli of varying duration. These multiple points thus make up a strength-duration curve which defines the muscle excitability for a single electrical pulse at different duration values (Fig. 5). It has long been noted that denervated muscles have a different response to short duration pulses than normal muscles. The chronaxie determination is only one point on the entire strength-duration curve and therefore gives somewhat less information than the entire curve. The chronaxie time represents the duration necessary for stimulus with a voltage twice the rheobase to elicit a muscle twitch. Chronaxie testing is a simple test and, although somewhat unreliable when compared to recent techniques, still can give useful information.

**The Main Tests.** In routine clinical electromyography, the main tests which have been found to have diagnostic importance are: 1) direct muscle

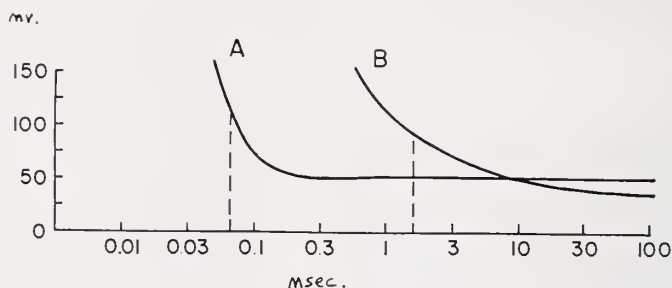


Fig. 5. Strength-Duration Curves of Muscles at the Motor Point. The motor point of a muscle is stimulated by electric shocks of varying durations as noted in the abscissa. The voltage needed to stimulate the muscle at these durations is plotted on the ordinate. The chronaxie value is only one point on this curve. Normal muscle (*A*) can be stimulated at short durations of 0.1 and 0.3 msec. Denervated muscle (*B*) can only respond to longer duration pulses. Chronaxie in muscle *A* is less than 0.1 millisecond, whereas in *B* it is over 1 msec. (From: Brock, S. and Krieger, H.: *The Basis of Clinical Neurology*. Baltimore: The Williams & Wilkins Company, 1963.)

recordings with needles; 2) conduction velocity studies of motor and sensory nerves; and 3) repetitive stimulation of motor nerves for neuromuscular junction studies. The other techniques such as H reflex studies, silent period recording, direct muscle stimulation, excitability curve of muscle, and neuromuscular junction studies are of great interest; however, at this time, they do not have any great clinical importance. The amount of research in various tests that can be done in electromyography is, in fact, so enormous that it would be worthwhile to consider the entire testing field as subdivided into a research area for the development of new tests and experiments, and a clinical area where tests of demonstrated value may be routinely employed.

## Diseases

An attempt will be made in this chapter to describe the findings of various techniques mentioned above in diseases of the human nervous system. Emphasis will be given to problems frequently encountered and the practical uses of electromyography as a diagnostic tool.

## **Diseases of the Upper Motor Neuron**

Involuntary movements caused by diseases of the brain such as tremor, athetosis, chorea, torticollis can be defined by recording the electrical potentials of the muscles by means of plate electrodes. The potentials recorded from these muscles are normal motor units firing in an involuntary abnormal sequence. The electromyographic criteria for these conditions is not well established and therefore the diagnostic importance of this type of recording is not very great. There is no characteristic electromyographic pattern in weakness caused by upper motor neuron disease. Usually, the number of motor units is decreased but each motor unit seen is of normal voltage and duration. The frequency of firing of each motor unit is increased, compared to the tension of the muscle. In feigned weakness or in inability to expend maximum effort because of local pain, the discharge frequency of individual motor units is less than that usually seen with maximal effort. The main difference between upper motor neuron weakness and lower motor neuron weakness is that the muscles in the upper motor neuron category do not show evidence of increased irritability or denervation. Fibrillations, positive waves, and fasciculations are not seen. When there is marked atrophy due to disuse or long standing upper motor neuron disease, there may be a decreased amount of insertion potentials but denervation phenomena are not seen. Studies of spinal cord reflexes such as the H reflex can be of some value in that these reflexes are at times more easily elicited in spastic conditions than in normal patients. Other studies of the motor nerves including conduction velocity and repetitive stimulation are within normal limits. The muscle strength-duration curves is also normal.

## **Diseases of the Lower Motor Neuron**

Electromyography finds its most common use in the diagnosis of lower motor neuron disease. Occasionally, the exact site of the abnormality of the lower motor neuron can be defined. One of the main findings in lower motor neuron disease as distinguished from upper motor neuron disease is the phenomena of denervation of the muscle. Denervation of the muscle entails a whole series of morphological, bio-chemical, and physiological changes which occur in a definite temporal order when the lower motor neuron is damaged or destroyed. Fasciculations are the first physiologic change noted when the lower motor neuron is damaged. This is most commonly seen in amyotrophic lateral sclerosis but can occur in other diseases. Fasciculations are high-voltage, polyphasic, .5 to 4 mv waves which occur spontaneously and irregularly. Fasciculations can be seen as twitching of the muscles and are thought to represent groups of motor units depolarizing synchronously. When greater damage is done to the lower motor neurons, a decrease in the number of motor units is seen. At this stage there is no change in the spontaneous electrical activity of the resting muscle. Two to three weeks after denervation, changes occur in the muscle tissue which are thought to be related to the degeneration of the terminal nerve fibers. The muscle becomes extremely irritable and depolarization of each individual muscle fiber can occur spontaneously or after mechanical irritation.

Fibrillations occur as spontaneous waves having an average duration of 1 to 2 milliseconds and with a regular frequency of 1 to 10 per second; the voltage is .05 to .5 mv; the form is usually diphasic or triphasic. These potentials are electrical phenomena and thus cannot be seen clinically. They probably represent a single muscle fiber depolarization. They are seen with any disease causing irritability of the muscle membrane which includes serum electrolyte changes, myopathy, and denervation. Positive waves are also seen at this time and they are defined as repetitive waves of 3 to 4 milliseconds duration, .05 to .5 mv amplitude, and having a sharp positive deflection followed by a slower return to the baseline. These waves also represent depolarization of single muscle fibers and have the same clinical significance as fibrillations. If the denervation of the muscle becomes a chronic condition, then the muscle will atrophy and eventually a decrease in the insertion potentials will be noted. In severe cases a complete fibrotic replacement of the muscle occurs and one may note absence of any electrical phenomena. In most cases, however, fibrillations and positive waves exist for many years.

When voluntary effort occurs there is a decreased number of motor units, which is similar to that seen in upper motor neuron disease. The presence of denervation potentials differentiates lower motor neuron disease from upper motor neuron disease, but repeated examinations may be necessary to establish the presence of denervation potentials which may occur 2 to 3 weeks *after* the onset of weakness.

Localization of the lesion affecting the lower motor neuron is occasionally possible. If all the muscles of a limb are affected, the evidence indicates diffuse involvement in the lower motor neurons. In localized disease the muscles affected may give the anatomical location of the lesion. For example, if the muscles showing denervation are innervated by one common root or one common nerve, then the evidence of disease of that root or nerve is established. The differentiation between root and peripheral nerve or plexus is sometimes possible by studying the paraspinal muscles. The posterior rami which supply the paraspinal muscle can help in localization because if the paraspinal muscles are involved, then the localized disease must be in the root since the posterior rami leaves the root before it enters the plexus. However, the absence of abnormality of the paraspinal muscles does not establish disease in the plexus or nerve because the absence of findings does not rule out disease. The muscle tissue studied in electromyography is a very small percentage of the total muscle and, therefore, one must be cautious of negative results in any evaluation.

The conduction velocity studies of motor nerve or sensory nerve as described above can help localize disease. Diseases of the anterior horn, root, or plexus do not as a rule give any change in conduction velocity of the motor or sensory nerve. This is true because mixed nerves are usually made up of at least two or three roots. In order to change the conduction velocity, which is a measurement of the *fastest* motor fibers, all of the motor fibers must be involved. On a practical basis, this only occurs in diseases of the nerve itself and not of the root or plexus. The normal conduction velocity of motor nerves is between 45 and 65 meters per second. In some diseases of the peripheral nerve, the con-



duction velocity is diffusely slow, although in other diseases only certain segments of a nerve may show abnormalities. The sensory nerve conduction studies may be the most sensitive index of peripheral neuropathies. At times the motor conduction velocity studies can be normal where as the sensory studies are abnormal, indicating primary involvement of sensory fibers. Muscle stimulation studies, such as the strength-duration curve show abnormalities in denervated muscles. As has been pointed out before, the denervated muscles are unable to respond to short duration electrical pulses. Therefore, the strength-duration curve is shifted, as shown in Figure 2. The chronaxie value will therefore be abnormal, with readings greater than one millisecond.

The combination of nerve stimulation studies with muscle recordings and muscle stimulation studies can make the exact location of the lesion of the lower motor neuron possible. The differentiation of lower motor neuron disease from myopathic disease is one of the most important areas of electromyographic diagnosis. This is a frequent clinical problem because the clinical findings are similar in both diseases. In both lower motor neuron disease and muscle disease there is frequently atrophic muscle with decreased reflexes and no sensory findings. In this situation the above tests can be of great aid.

### **Neuromuscular Junction Disease**

The most common disease of the neuromuscular junction is myasthenia gravis. However, drug intoxication, poisoning, and some insect bites all may affect this area. Recently, the syndrome of myasthenia gravis associated with carcinoma of the lung, which also involves the neuromuscular junction, has been established. In these diseases, studies of the motor units described above may show a decrease in voltage or number of motor units on voluntary effort. This is most pronounced after one or two minute effort. This type of test is unreliable because the patient's cooperation is necessary and there is always the reservation that maximal effort was not expended. An increase in motor unit activity after drugs such as Tensilon may be of aid in establishing the diagnosis of myasthenia gravis. The conduction velocity of motor and sensory nerves is within normal limits in these diseases. Repetitive stimulation studies extensively described by many workers have usually used the ulnar-hypothenar muscle system. The response to repetitive stimulus of 3 to 25 per second is frequently abnormal in myasthenia gravis with a decrease in the total muscle response noted after the third or fourth stimulus. The response of this type of testing to intravenous and intra-arterial drugs can also be helpful in diagnosis of the disease. In the myasthenia syndrome associated with carcinoma of the lung, an entirely different set of responses is seen with repetitive stimulation. In contradistinction to the results in myasthenia gravis, the later stimuli in the train show a greater muscle electrical response than to the first or second stimulus. The disease has been defined in terms of this response to electromyographic testing.

### **Myopathy**

This category of disease includes a large number of poorly defined entities with various etiologies.



Needle studies of muscles in these diseases reveal varying results, depending upon the type of muscle disease and the severity of the myopathy. The muscle at rest usually does not show irritability or denervation potentials, as described in the section on lower motor neuron disease. The exceptions to this rule are:

- 1) Polymyositis, where fibrillations, positive waves, and high frequency bizarre potentials are frequently seen.
- 2) Myotonic dystrophy, where extreme membrane irritability is noted with repetitive oscillation of the membrane potential causing the typical myotonic or "dive bomber" electromyographic response at rest.
- 3) In some cases of muscular dystrophy, especially the pseudohypertrophic type, fibrillations and myotonic-like phenomena can be seen.

The most important criteria for myopathy is in the analysis of individual voluntary motor units. In all myopathies that are severe, a tendency for the motor units to be of shorter duration will be noted. The forms of the units tend to be polyphasic and the voltage low. The frequency of firing of each motor unit is greater than normal for the muscle tension measured. The total number of motor units is increased when compared to the muscle tension measured. In mild and moderate myopathies the changes in the duration of motor units is difficult to establish without a detailed analysis of many motor units. This type of examination is not suitable to routine clinical work and therefore the electromyographer may have a difficult time determining abnormalities in some cases of clinical myopathy.

The other tests described in the section on methods are generally within normal limits in myopathic disease.

### SUMMARY

Electromyography consists of many different types of tests. The important clinical tests in electromyography and the meaning of the various results are reviewed. In many areas electromyography has been overused, and too often definite diagnoses are made with little evidence. An attempt is made here to disregard negative or equivocal findings in electromyographic recordings. Definite abnormal findings which are meaningful in diagnosis of disease states are the important phenomena. Electromyography, when used with extreme caution, can be of value in localizing disease in clinical neurology.

# Brain Scanning

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## Introduction

Brain scanning is a new diagnostic technique which depends upon the differential uptake of radioactive substances by diseased intracranial tissue and the detection of this locus by suitable instrumentation. The reliability of radioisotope examinations as an index of the presence of a variety of pathological conditions has been amply documented by clinical experience with the examinations over the past decade. Neoplasms, hematomas, abscesses, arteriovenous malformations and infarctions secondary to occlusive vascular phenomena are the types of disease processes most frequently detected with radioisotopes. Since many types of pathological lesions take up radioactive tracer substances readily, specific diagnosis by means of brain scanning alone is hazardous.

The major concentrations of radioactivity visualized on the normal brain scan are localized to the soft tissues and vasculature of the cranium. Normal brain tissue takes up relatively little of the tracer agents commonly used for diagnostic scanning (Figs. 1, 2).

## Clinical Importance

Brain scanning is most useful as a screening procedure in the evaluation of patients suspected of harboring intracranial pathology. It is particularly valuable in cases where clinical signs and symptoms do not indicate clearcut involvement of one side of the brain or the other.

Since the entire brain can be examined at the time scanning is performed, clinically unsuspected areas may be implicated as pathological. Scanning may not only lateralize pathology, but may demonstrate that multiple areas of disease exist.

The following case history will illustrate the role that brain scanning played in the diagnosis and management of a patient with a clinically unlocalized neurological picture:

A 65 year old man presented with confusion and memory loss. There was no evidence of focal neurological disease, and the patient was otherwise in good health. Blood chemistries and x-rays of the chest and skull were normal. An EEG indicated a diffuse abnormality. The CSF revealed a moderately elevated protein content. A right brachial angiogram was considered to be within normal limits.

A brain scan demonstrated the presence of two lesions; one in the left frontal region and the other on the left side of the posterior fossa (Fig. 3).

A left carotid angiogram confirmed the presence of an avascular mass in the left frontal region. Surgery was proposed, but in view of the findings of the brain scan, a pneumoen-

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cephalogram was performed. This study confirmed the presence of the second lesion on the left side of the posterior fossa.

A presumptive diagnosis of metastatic disease was made, and the patient was treated with radiotherapy.

Repeat radioisotope and contrast studies six weeks later demonstrated a slight decrease in the size of both lesions.

Brain scanning is a benign procedure and can be performed in situations

THE MOUNT SINAI HOSPITAL  
NEW YORK

RADIO-ISOTOPE  
BRAIN SCAN REPORT


Name/Sex/Age

Location  
Hosp. No.

Attending  
Physician

ISOTOPE:  
AMOUNT INJECTED:  
DATE INJECTED:

DATE(S) SCANNED:  
SCAN NUMBER:  
DATE OF REPORT:

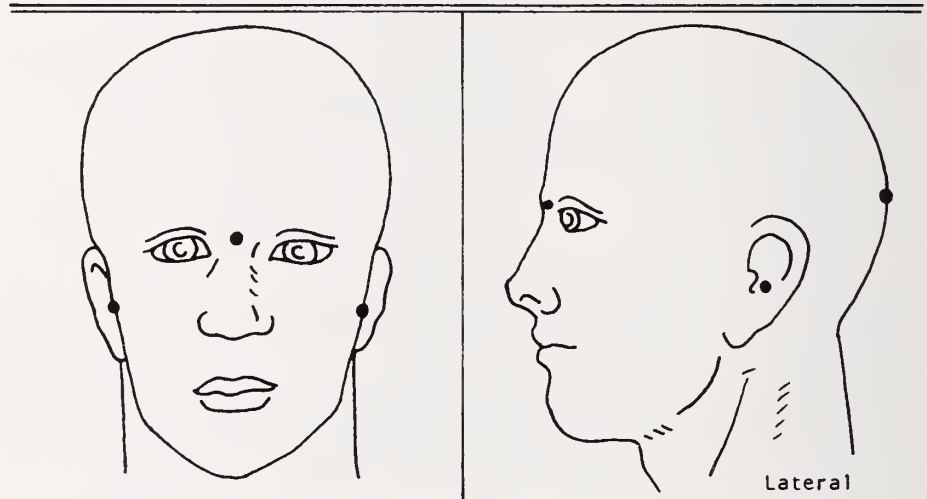


FIG. 1. Report form illustrating anterior and lateral scan positions with landmark dots. All lateral scans are shown facing to the right as in the diagram.

where more rigorous testing is precluded by the patient's clinical condition, or where the index of suspicion is not sufficiently high to warrant the exploratory use of contrast studies to rule out the presence of demonstrable intracranial pathology.

Because of the high incidence of neoplasms and other types of mass lesions in patients with abnormal radioisotope studies, positive scans are usually followed by contrast studies which may help elucidate the nature of the abnormality visualized by brain scanning.

A positive scan may be the only indication that further diagnostic testing will be worth the risk. The following case history is illustrative since a diagno-

sis would probably not have been readily established without the use of the brain scan:

A 54 year old woman was hospitalized complaining of nausea and vomiting. Seven years previously she had undergone removal of an acoustic neuroma. Aside from her complaints, there was no evidence on neurological examination to suggest regrowth of the tumor. When the patient improved dramatically with bedrest and intravenous fluid therapy,

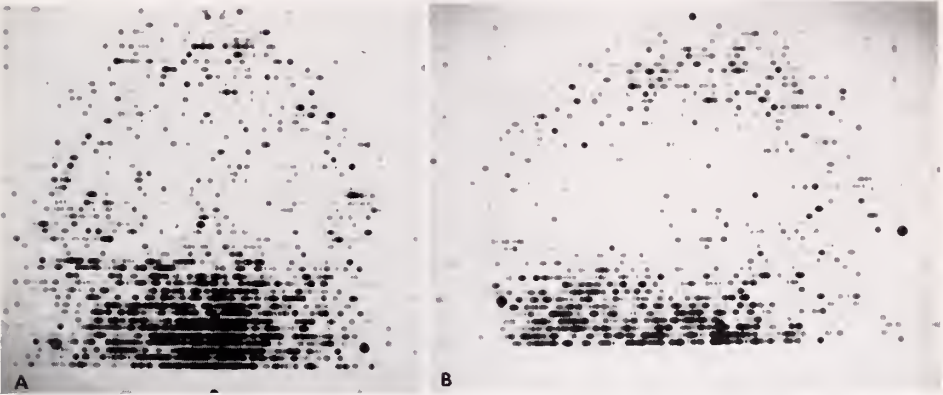


FIG. 2. Normal delayed (48 hr.) scans (A) anterior and (B) lateral.

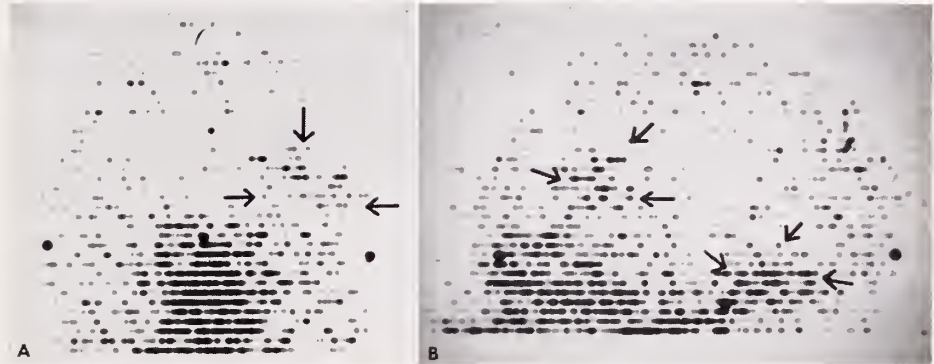


FIG. 3. Forty-eight hour scans (A) anterior and (B) left lateral in a patient with lesions in the left frontal region and left posterior fossa (arrows).

her physicians were loath to repeat the contrast studies which had led to her original operation.

A brain scan was performed which demonstrated a lesion on the right side of the posterior fossa, the site of her prior pathology (Fig. 4).

In view of the brain scan findings, it was decided to perform a small posterior fossa air study to rule out regrowth of the tumor. The findings of the PEG were abnormal, confirming the brain scan.

At operation, a large, recurrent cystic tumor was removed.

The most unique use of brain scanning is for follow-up studies. Scanning may be performed as a follow-up measure in patients who have undergone neuro-

surgery or have had radiation therapy. Scans performed over a period of weeks or months may be particularly valuable in the management of cases where the diagnosis is inconclusive. Since hospitalization is not required, and since most patients have no objection to repeated radioisotope examinations, studies are easily accomplished on an out-patient basis. The level of radiation exposure can be held within such limits that no ill effects will result.

Brain scanning may indicate a focal or a diffuse abnormality during the more acute phase of an illness suspected of being due to cerebro-vascular dis-

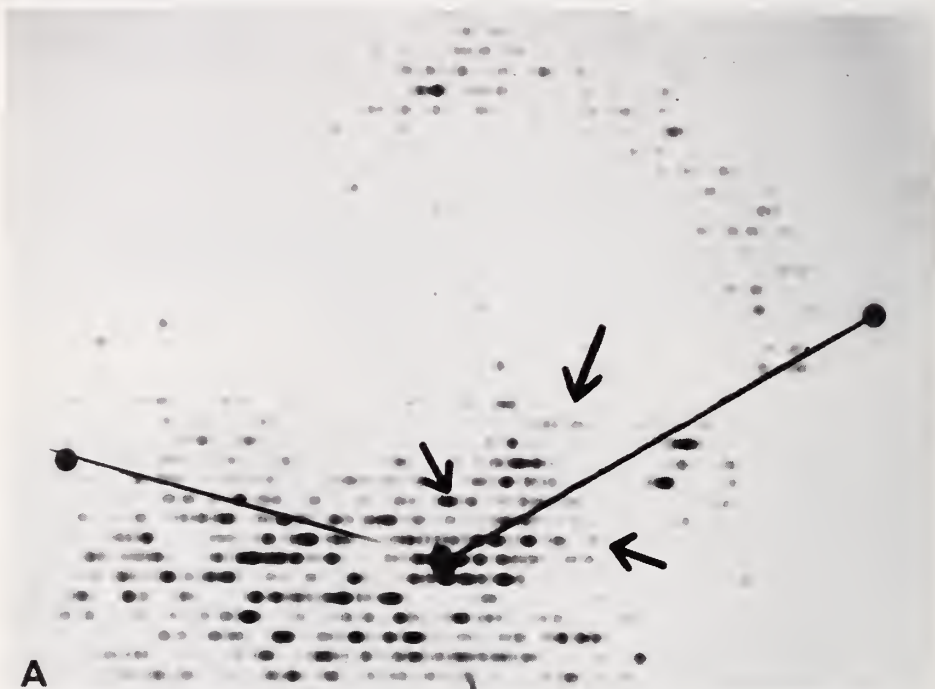


FIG. 4. Forty-eight hour right lateral scan in a patient with a recurrent acoustic neuroma (arrow).

ease. In-hospital studies such as angiography may demonstrate the occlusion of a specific blood vessel in some cases, yet in other cases contrast studies demonstrate no more than evidence of a generalized arteriosclerosis, and the patient may remain a tumor suspect. In such cases, disappearance of the abnormality visualized on the scan may help to rule out the presence of a mass lesion.

Recurrence or persistence of an abnormal scan may be of prognostic value in the management of patients, particularly when the clinical picture is misleading.

Two patients with abnormal brain scans and confirmatory contrast studies were followed by repeated brain scanning. One patient was treated with radiation therapy and became asymptomatic. The EEG also returned to normal. Repeat scan during this period demonstrated the lesion as seen on the original scan. The patient deteriorated subsequently. A metastatic lesion was found in the appropriate location at the time of necropsy.



The second patient improved markedly without any therapy at all and became asymptomatic. The diagnosis of an intracranial lesion was in doubt clinically despite the fact that her in-hospital studies were abnormal. Repeat scan again confirmed the lesion as originally seen. The patient soon succumbed; at necropsy a glioblastoma was found.

Radioisotope studies may be indicated even after the presence of a lesion has been demonstrated by more conventional studies. Localization of intracranial lesions by means of brain scanning may often be superior to the results achieved by means of angiography or pneumoencephalography.

In angiography, the location of the pathology must be deduced from the displacement of normal vascular structures in the absence of a "tumor stain" or conglomeration of abnormal blood vessels. Localization of a lesion by means of pneumoencephalography is dependent on the displacement of the gas-filled ventricular system, cisterns, or sulci from their normal positions. Except where

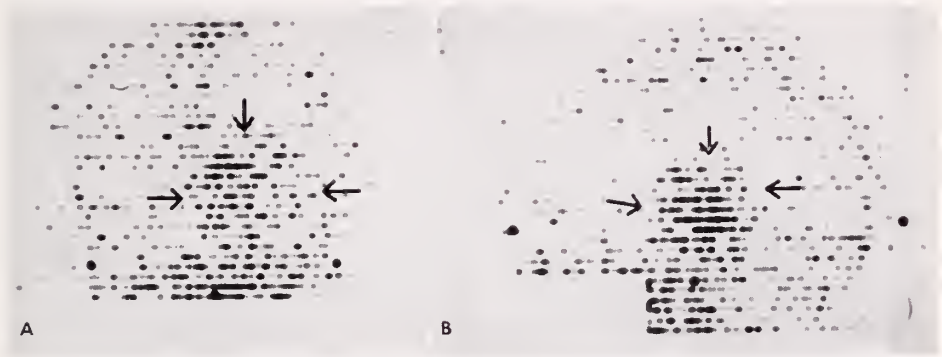


FIG. 5. Forty-eight hour scans (A) anterior and (B) left lateral in a patient with an astrocytoma involving the left thalamic region. The scans were used for localization purposes at the time of needle biopsy. Angiography indicated a deep avascular lesion.

air actually outlines a lesion, pneumoencephalography may give only a relatively gross idea of its exact location.

An abnormal concentration of radioactivity as visualized on the brain scan indicates the actual site of an intracranial disease process. In cases where angiography demonstrates the presence of an avascular lesion, an abnormal scan showing a focal, well circumscribed lesion may be of exceptional localizing value, particularly if a needle biopsy through a burr hole is planned (Fig. 5).

Occasionally, depending on the size and location of a particular lesion, brain scanning may be positive when angiography or pneumoencephalography are negative or indefinite. Ventriculography may be necessary to confirm an abnormality visualized on the brain scan in cases of midline lesions which obstruct the ventricular system (Fig. 6).

### Limitations

Although the abnormal brain scan almost always indicates the presence of a pathological process, the negative scan, on the other hand, does not offer the

same degree of assurance that pathology is absent. Brain scanning is often ineffective in a small percentage of cases where low grade gliomas or infiltrating types of neoplasms are present. In addition, certain intracranial mass lesions, depending on their size and location, are particularly liable to elude detection by brain scanning.

Lesions smaller than two to three centimeters in diameter are usually beyond the resolution of current instrumentation and often only the largest of many discrete metastatic foci may be detected. Posterior fossa lesions are frequently overlooked both because of their small size and the fact that they are difficult to distinguish from their rather considerable background of radiation localized in vascular and soft tissue structures.

A similar situation contrives to make detection of lesions involving the floor of the cranial fossa equally difficult even when these lesions are relatively

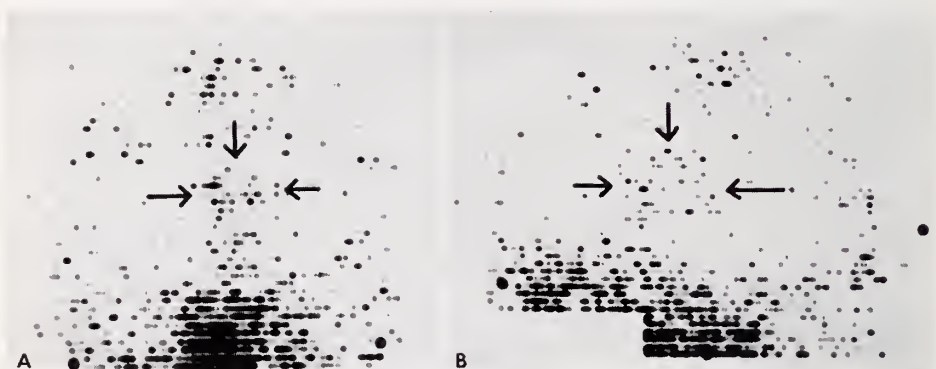


FIG. 6. Twenty-four hour scans (A) anterior and (B) left lateral in a patient with a glioblastoma of the corpus callosum. The lesion was confirmed with ventriculography. Angiography was non-specific in this case.

large. For this reason, pituitary and parasellar tumors, as well as other types of extra-dural growths such as chordoma and craniopharyngioma are probably better visualized by other methods of examination.

Despite these minor limitations, the negative brain scan is still of considerable value and may play an important role in the management of the patient with suspected intracranial disease.

The major limitation of the diagnostic usefulness of the radioisotope examination is the current inability of this technique to specify the nature of the pathological process it does detect. Any of a variety of intracranial conditions varying from the most benign to the most malignant types of disorders may make themselves manifest by reflecting an increased concentration of radioisotope.

Although there are sometimes striking differences with regard to the rate of uptake and order of concentration of tracer agents by different types of lesions, specific diagnosis solely by means of brain scanning with radioisotopes remains a controversial matter.

## Historical Aspects and Present Status

George Moore first demonstrated that localization of intracranial neoplasms by means of radioisotopes was possible in 1947. After discovering that intravenously administered fluorescein accumulated in pathological intracranial tissues, Moore tagged this dye substance with a gamma-emitting radioisotope and attempted to determine the resulting locus of radioactivity with a Geiger-Mueller counter. By 1951, with somewhat improved instrumentation, he was able to localize 17 of 26 verified intracranial neoplasms.

At first, in the hands of other investigators, the results of brain scanning were much less encouraging. However, the use of more effective tracer substances, beginning in 1951 with radio-iodinated serum albumin (RISA), and more sophisticated scintillation counters and recording devices, has served to confirm Moore's original impression regarding the diagnostic value of radioisotope examinations.

Today a variety of tracer agents and scanning devices are available for clinical brain scanning. The overall results indicate that the choice of tracer agent or type of equipment does not materially influence the diagnostic accuracy of the test. Meningiomas, glioblastomas, and metastatic deposits have all been detected with a universally high degree of accuracy. Conversely, lesions at the base of the skull or in the posterior fossa which are obscured by background radioactivity, and cystic lesions and low grade gliomas which do not take up sufficient concentrations of tracer agent to permit detection have eluded diagnosis by this method regardless of the tracer agent or instrumentation employed. The use of more sensitive detection devices combined with higher concentrations of radioactivity derived from ultra-short lived radioisotopes may solve some of these problems. The development of new tracer substances with specific affinities for different pathological entities would be of even more importance.

## SUMMARY

Brain scanning with radioisotopes has proved to be an effective technique for the detection and localization of a variety of intracranial lesions. The added fact that brain scanning is a benign procedure suitable for out-patient screening and follow-up studies makes it of great value to the clinician involved in the diagnosis and management of intracranial disease.



# **The Neuroradiological Examinations**

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## **INTRODUCTION**

Neuroradiology, the roentgenographic study of the nervous system, is a relatively new subspecialty which has greatly altered the diagnosis and treatment of diseases of the brain and spinal cord. In the past, diagnosis depended upon the neurologist's clinical experience and acumen and very often required exploratory surgery for a more precise answer. Too often the pathologic process remained obscure or was diagnosed incorrectly. Today, neuroradiology offers the most accurate diagnostic method for the detection and localization of lesions of the nervous system. It often uncovers the etiology as well.

Whereas previously described laboratory examinations such as electroencephalography, electromyography, and brainscanning are screening tests which can be performed on an outpatient basis, the neuroradiologic procedures require hospitalization. However, in view of the valuable information that cerebral angiography and/or pneumoencephalography yield at so small a risk, the neurologist should not hesitate to perform them when he suspects the presence of a structural lesion. It is as important to learn that there is no lesion of the nervous system (as shown by negative neuroradiologic studies) as it is to determine the existence of one. The neurologist thus informed as to the structure and function of the patient's nervous system can more rationally diagnose and manage the patient.

The following is a brief introduction to the indications, techniques, and interpretation of the neuroradiologic examinations.

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## NON-CONTRAST EXAMINATIONS

### PLAIN SKULL FILMS

The routine films of the skull should always be performed first since they may demonstrate abnormalities which direct the examiner to the next more definitive radiologic procedure. A description of all the defects visible on skull films would require a separate chapter but they may be classified in terms of:

1. Structural abnormalities
2. Abnormal radiodensities
3. Abnormal radiolucencies

**Structural Abnormalities.** The configuration and size of the skull are considered within this category as are the appearance of the fissures, fontanelles, foramina, sutures, cranial fossae, and base of the skull. Abnormalities in this category include: craniostenosis, macrocephaly, erosion of the optic and acoustic foramen, enlargement of the sella turcica and platybasia.

**Abnormal Radiodensities.** Brain tumors such as meningiomas (Fig. 1) and gliomas (Fig. 2) may be calcified. Calcifications may also be seen in non-neoplastic lesions such as vascular malformations and hematomas.

Proliferative bony changes in the skull are commonly associated with superficially placed tumors such as meningiomas; however, thickened bone or hyperostosis may also be seen in fibrous dysplasia and hyperostosis frontalis interna. Metastatic lesions to the skull such as from breast, lung or prostate result in localized osteoblastic areas of increased radiodensity.

**Abnormal Radiolucencies.** Erosion of the skull is frequently seen with convexity meningiomas; enlargement of the meningeal vascular channels is often present in addition (Fig. 3). Metastatic tumors to the skull often cause localized areas of bone destruction as may blood dyscrasias. Primary lesions of the skull such as epidermoids, eosinophilic granuloma, and hemangiomas (Fig. 4) produce characteristic radiolucent defects. Fractures characteristically appear as linear radiolucent streaks.

### Standard Views of the Skull

Standard x-rays of the skull include the following views:

**The Lateral View.** (Fig. 5) This view provides excellent visualization of the position of the calcified pineal gland, the sella turcica, and anterior and middle cranial fossae.

**The Straight Posterior-Anterior View.** (Fig. 6) Midline displacement of the pineal is best seen in this view. This view also offers excellent visualization of the porus acousticus projected through the bony orbits.

**The Inclined Posterior-Anterior (Caldwell) View.** (Fig. 7) The sphenoid ridge, roof of the orbit, and floor of the sella tureica are well visualized in this projection.

**The Inclined Anterior-Posterior (Towne) View.** (Fig. 8) The structures within the posterior fossa such as the petrous pyramids, internal acoustic canals and foramen magnum are best defined by this projection.

### **Special Views of the Skull**

When the clinical history and neurologic examination warrant additional views, special projections of the skull are obtained. These include optic foramen, internal auditory canal, stereoscopic base, and jugular foramen views. Both right and left sides should always be x-rayed so that minor changes between the abnormal and normal sides are discernible.

## **PLAIN SPINE FILMS**

Routine x-rays of the spine are indicated to determine the location and etiology of a variety of clinical conditions which unsuspectingly involve the spine or its contents. So-called sciatic pain may be due to a cauda equina tumor. Chest pain or atrophy of the muscles of the hand may result from the encroachment of osteophytes on intervertebral foramina in the neck. Symptoms and signs in the lower extremities such as foot drop may result from a herniated disc of the lumbosacral spine. Arthritis and/or ridging of the cervical spine frequently produces motor or sensory symptoms referable to the cervical level or a level well below. Thus weakness of the legs with or without sphincter disturbances may be secondary to arthritis of the cervical spine. Spasticity and sensory loss in the legs can occur from a meningioma of the thoracic cord. In general, it is important to examine the spinal structures well above the clinically indicated level.

The routine films of the spine detect the presence of abnormalities of the vertebral bodies, intervertebral disc spaces, and nerve root foramina. Films are obtained in the anterior-posterior, lateral, and oblique projections. The anterior-posterior projection visualizes the pedicles, lamina and framework of the vertebral bodies. The lateral view visualizes the intervertebral disc spaces, curvature and alignment of the vertebral bodies and the spinous processes. This view thus demonstrates degenerative changes of the spine such as narrowing of the intervertebral disc space, osteophyte formation, osseous bridging and bony sclerosis (Figs. 9 and 10). The oblique view visualizes the intervertebral foramina, and in the lumbar spine the pars interarticularis. This view thus demonstrates encroachment upon the intervertebral foramina, or erosion as from a neurofibroma (Fig. 11).

A negative x-ray examination of the spine does not exclude the existence of pathology of the cord or nerve roots; moreover, repeat films at a later date may demonstrate an abnormality.

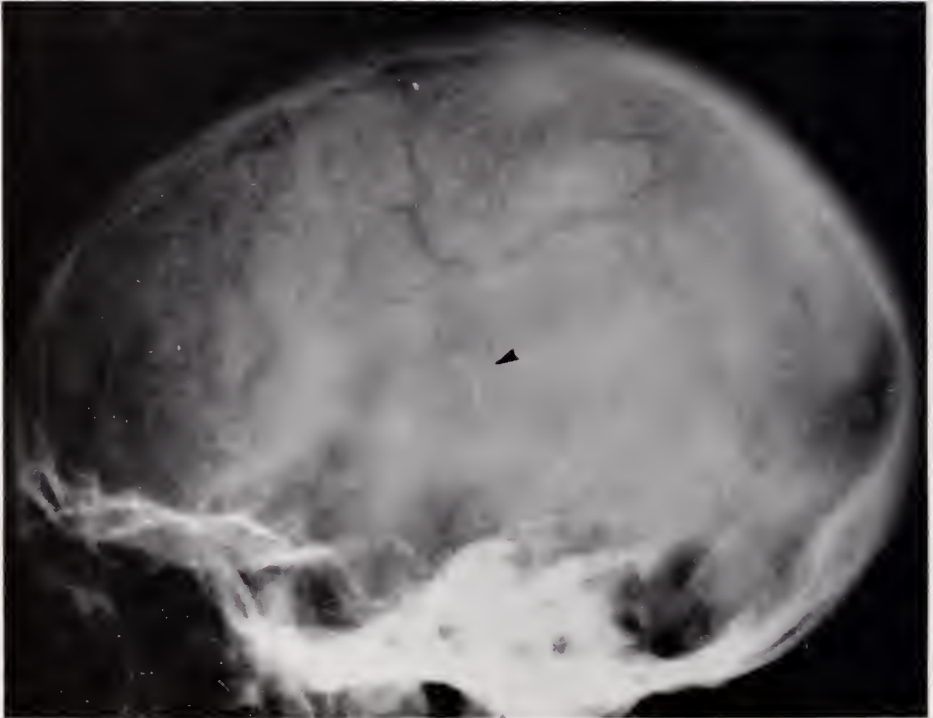
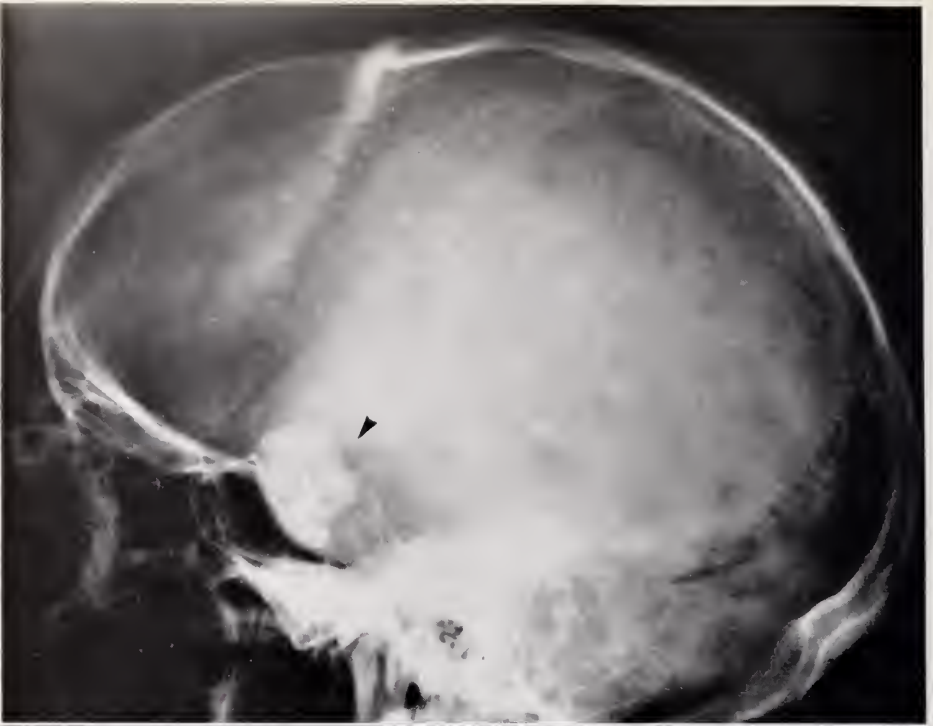


FIG. 1. **Abnormal Radiodensity.** Calcification within a meningioma.

FIG. 2. **Abnormal Radiodensity.** Calcification within an astrocytoma.

#### Abnormal Radiodensities

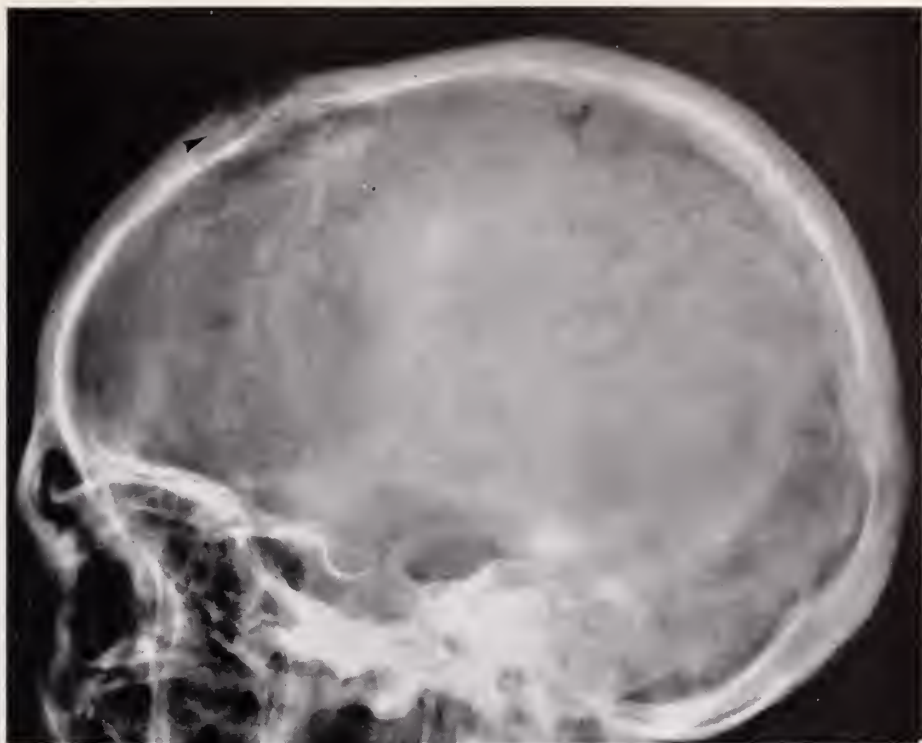


FIG. 3. **Abnormal Radiolucency.** Erosion of the skull and enlargement of vascular channels—meningioma.

FIG. 4. **Abnormal Radiolucency.** A circumscribed circular erosion—heman-  
gioma.

#### Abnormal Radiolucencies





FIG. 5. **The Lateral View.** The pineal gland (P), sella turcica (ST), anterior clinoid (AC) and posterior clinoid (PC) processes, and planum sphenoidale (PS).

FIG. 6. **The Straight Posterior-Anterior View.** The pineal gland (P), internal acoustic canal (IAC) and the anterior clinoid process (AC).

### Standard Views of the Skull



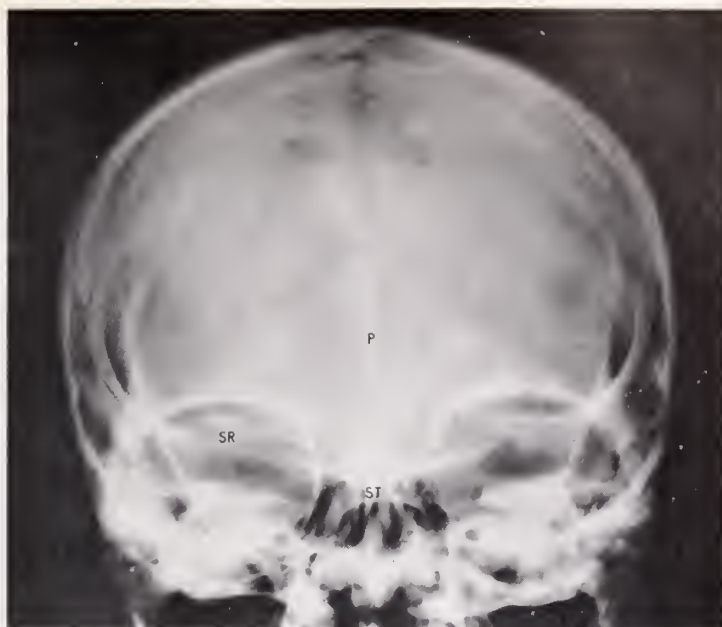


FIG. 7. **Inclined Posterior-Anterior (Caldwell) View.** The sphenoid ridge (SR), floor of the sella turcica (ST), and pineal gland (P).

FIG. 8. **Anterior-Posterior, Half Axial (Towne) View.** The petrous pyramid (PP), foramen magnum (FM) and pineal gland (P).

#### Standard Views of the Skull



FIG. 9. **Abnormalities on Lateral View of Cervical Spine.** Narrowing of disc space (C5-C6) and reversal of the normal cervical curvature.



FIG. 10. **Abnormalities on Lateral View of Cervical Spine.** Osseous bridging (A), bony sclerosis (B), osteophyte (C), narrowing of disc space (D).

#### Abnormalities on Lateral Cervical Spine Films



FIG. 11. **Abnormality on Oblique Cervical Spine View.** Erosion of an intervertebral foramen (C6-C7)—neurofibroma.

## CONTRAST EXAMINATIONS

### CEREBRAL ANGIOGRAPHY

The injection of radiopaque contrast material into the arteries of the neck or arm results in excellent visualization of the intracranial vessels thus demonstrating the anatomy and physiology of the cerebral circulation. Any changes from their normal appearance or circulation provides information as to the presence of a structural abnormality. Neoplasms, infectious processes, atherosclerotic disease, and degenerative changes of the brain produce characteristic abnormalities on the cerebral angiogram. Mass lesions of the brain displace and distort neighboring vessels and the normal pattern of cerebral circulation. Atherosclerotic and other vascular diseases produce changes in blood flow and structural deformities of the vessels themselves which are observable on the x-ray. Alterations in the appearance of the ventricular system can be indirectly determined by studying the arteries and deep veins adjacent to the ventricles.

Prior to angiography the neurologist depended upon direct surgical biopsy or an autopsy examination to determine the etiology of many structural brain diseases. The advances in arteriography have made the clinical-neuroradiological correlations as informative as the clinical-pathological. Particularly when the clinical information is slight or non-specific, angiography may detect the site and etiology of the lesion.

#### The Procedure

The angiogram is performed in the radiology department under the supervision of a physician. At the time of injection the patient will experience a transient burning sensation in the distribution of the injected vessels. A percutaneous puncture of the carotid or brachial artery is performed, 3 cc of contrast media injected, and a rapidly developed Polaroid film taken (Fig. 12). This shows the position of the needle within the vessel and avoids injection into the sheath of the artery or outside of its lumen. When the needle is properly positioned an automatic injector is utilized for sustained and even injection under pressure. Serial films of the cerebral circulation are taken with a rapid film-changing device so that the arterial, intermediate, and venous phases are obtained. Films are taken in the anterior-posterior and lateral projections. Depending on the area of the brain and/or blood supply to be studied an injection of either the carotid or the brachial artery is performed.

**Carotid Versus Brachial Injection.** Injection of the left or right carotid artery visualizes only the anterior circulation of the brain on the side injected, *i.e.* the anterior and middle cerebral arteries (Figs. 13 and 14); occasionally the posterior cerebral artery also fills.

An aortic arch study (Fig. 15) shows the normal anatomy of the vessels arising from the arch of the aorta. Since retrograde (pressure) injection of the left brachial artery fills only the left vertebral artery the posterior circulation of the brain is the only part visualized, *i.e.* left vertebral, basilar, left and right cerebellar and posterior cerebral arteries (Fig. 16). A retrograde right brachial injection, however, fills both the right carotid and right vertebral arteries thus visualizing both the anterior and posterior circulations (Fig. 17). However, due to overlapping of blood vessels in the anterior-posterior view visualization of the anterior circulation is best achieved by direct injection of the appropriate carotid artery (Fig. 14). If the contralateral carotid artery is manually compressed during the course of a carotid injection the intracranial vessels on both sides will be visualized (Fig. 18). The posterior circulation is visualized best by a left brachial injection or by direct injection of the vertebral artery. Although the complications from cerebral arteriography are few the danger and discomfort is considerably less when the brachial artery is the site of injection.

### Abnormal Radiologic Findings

A simplified classification of the abnormal findings on cerebral angiography includes:

1. Vessel abnormalities
2. Alterations in cerebral circulation
3. Vessel displacements

**Vessel Abnormalities.** Narrowing or occlusion of vessels of the neck or head frequently cause neurologic symptoms referable to distant parts of the brain. The cerebral angiogram gives information as to the patency of these vessels as well as a dynamic view of their circulation. Stenosis or occlusion of the carotid (Fig. 19) or other arteries (Fig. 20) may be responsible for poor circulation in any of the cerebral arteries or their branches.

Localized collections of abnormal vessels may appear as a stain, blush, or as an irregular persistent collection. These abnormalities localize the exact site of the lesion and often indicate its etiology. Characteristic collections of abnormal vessels characterize metastatic lesions (Figs. 21 and 22), glioblastomas (Fig. 23), and meningiomas (Fig. 24). Local deformities of vessels such as spasm, narrowing and dilatation (aneurysm) are also evident on arteriography. Arterio-venous malformations (AVM) are also included in this category (Fig. 25).

**Alterations in Cerebral Circulation.** The cerebral blood flow may be increased, decreased, or absent. In malignant brain tumors there is early filling of the veins indicating arterio-venous shunting. With increased intracranial pressure or atherosclerosis the circulation time is delayed so that there is a prolongation of the arterial phase. With occlusion of blood vessels there is an absence or paucity of filling. When the major vessels or their branches are occluded collateral or retrograde filling may occur.



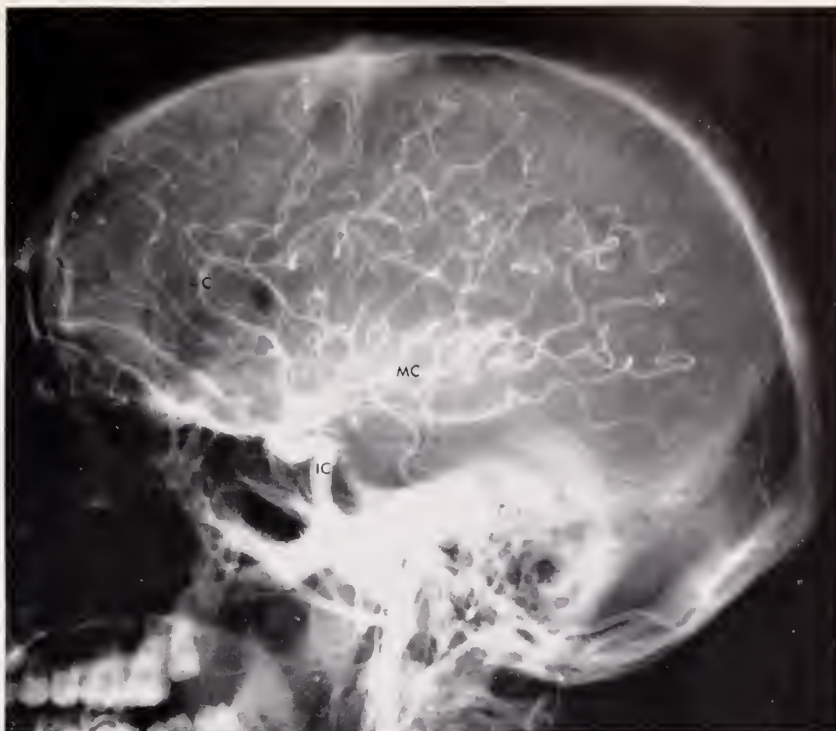
**Displacement of Vessels.** The anterior cerebral artery is a midline structure and displacement of this vessel indicates the presence of a mass lesion (Fig. 26). The middle cerebral artery is more laterally placed and its branches form the angiographic Sylvian triangle (Figs. 27 and 28). Displacement of this triangle whether downward, forward or upward indicates the location of the mass (Figs. 29, 30, 31, 32). Subdural hematomas characteristically appear as an avascular area beneath the calvarium and displace the underlying vessels as well as the anterior cerebral artery across the midline (Fig. 33). In addition to gross displacements, local deformities of vessels such as stretching or bowing indicate the presence and location of a mass lesion (Fig. 34). The internal cerebral vein is a deep midline structure (Fig. 35) and displacement of this vessel either laterally, up, or down is a sensitive indicator of a mass lesion (Fig. 36).



**FIG. 12. Polaroid Film of Percutaneous Puncture of Right Common Carotid Artery.** Three cc of contrast media have been injected and a rapidly developed film (Polaroid) taken. The needle tip is seen in proper position within the lumen of the carotid artery.

### The Normal Carotid Angiogram

*(See facing page)*



**FIG. 13. Right Carotid Injection (lateral view) Visualizes the Anterior Circulation.** The internal carotid (IC), middle cerebral (MC), and anterior cerebral (AC) arteries are visualized during a carotid injection.

**FIG. 14. Right Carotid Injection (anterior-posterior view) visualizes the Anterior Circulation.** The internal carotid (IC), anterior (AC), and middle cerebral (MC) arteries are shown in the frontal projection.



**FIG. 15. Normal Vessels Arising From the Aortic Arch.** An aortic arch study visualizes the left vertebral (LV), left common carotid (LCC), right vertebral (RV), and right common carotid (RCC) arteries.

**FIG. 16. Left Brachial Injection (lateral view) Visualizes Only the Posterior Circulation.** The injection of the left brachial artery fills the left vertebral (V), basilar (B), left posterior inferior cerebellar (PIC), left and right superior cerebellar (SC) and posterior cerebral (PC) arteries.

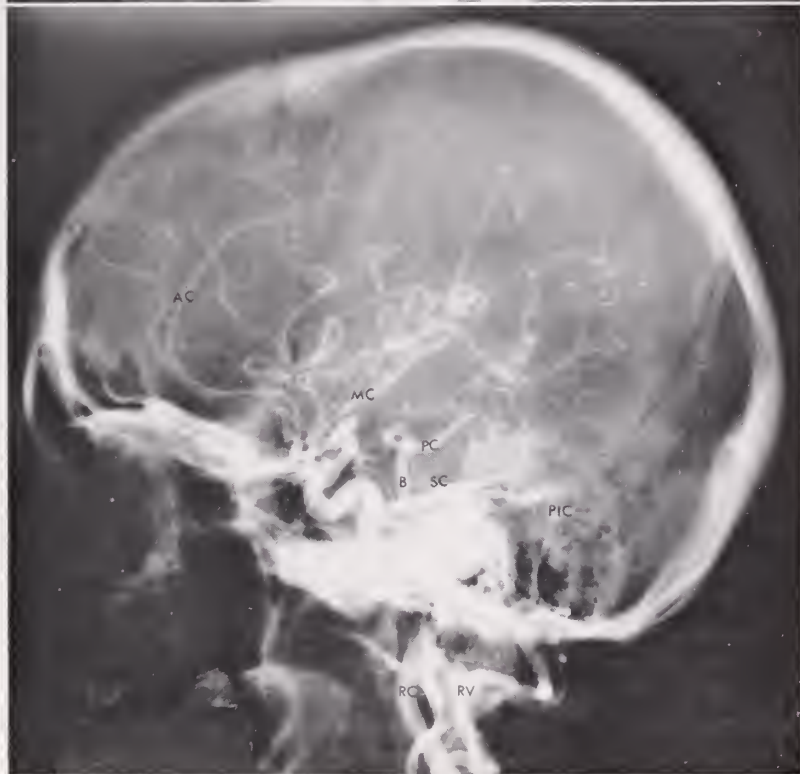


FIG. 16. (For caption see bottom facing page.)

**FIG 17. Right Brachial Injection (lateral view) Visualizes Both the Anterior and Posterior Circulations.** The anterior circulation filled from the right carotid (RC) artery includes the anterior cerebral (AC) and middle cerebral (MC) arteries. The posterior circulation includes right vertebral (RV), right posterior inferior cerebellar (PIC), basilar (B), superior cerebellar (SC) and posterior cerebral (PC) arteries.

#### The Normal Left and Right Brachial Angiograms





FIG. 18. **Left Carotid Injection with Contralateral Compression in the Neck.** The anterior and middle cerebral (MC) arteries are visualized on the right side in addition to the normal filling of these arteries on the injected (left) side.





FIG. 19. Stenosis of the Internal Carotid Artery in the Neck. (left carotid angiogram).

FIG. 20. Occlusion of the Internal Carotid Artery Prior to the Origin of the Anterior and Middle Cerebral Arteries (right brachial angiogram).

#### Vessel Abnormalities



FIG. 21. Stain: Metastatic Lesion (anterior-posterior view).

FIG. 22. Stain: Metastatic Lesion (lateral view).

#### Vessel Abnormalities



FIG. 23. Stain: Glioblastoma (lateral view).

FIG. 24. Stain: Meningioma (lateral view).

#### Vessel Abnormalities

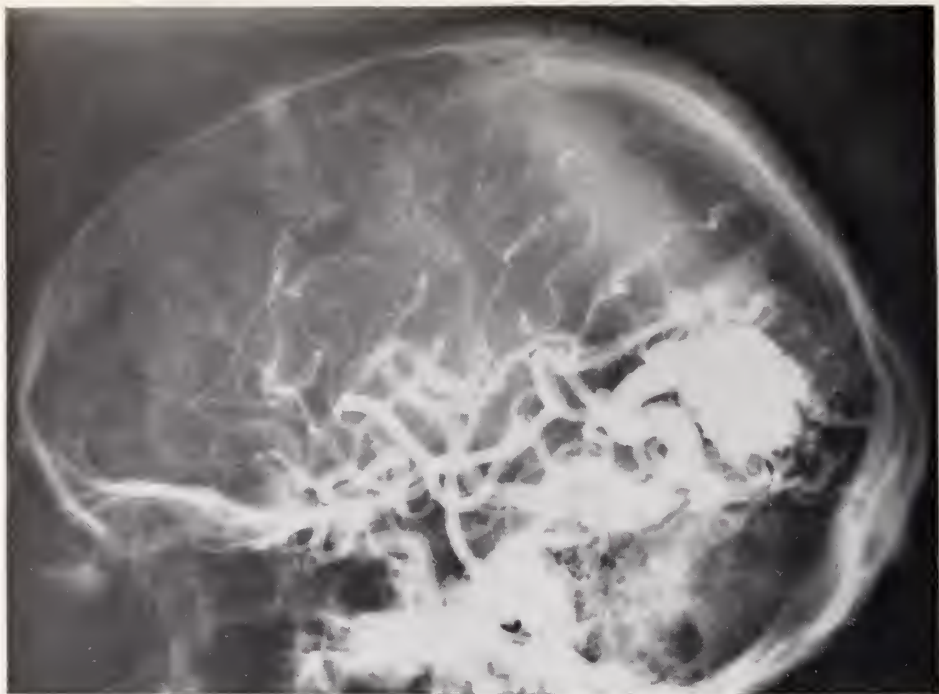


FIG. 25. **Arterio-Venous Malformation** (right brachial angiogram).

FIG. 26. **Displacement of the Anterior Cerebral Artery** (left carotid angiogram). A left frontal tumor has displaced the anterior cerebral artery (AC) across the midline to the opposite side.





FIG. 27. **Lateral View of the Normal Sylvian Triangle** (left carotid angiogram). The Sylvian Triangle (A,B,C) is formed by the middle cerebral artery (MC) and its branches.

FIG. 28. **Anterior-Posterior View of the Normal Sylvian Triangle** (left carotid angiogram). The Sylvian Triangle as seen in the frontal projection.

### The Normal Angiographic Sylvian Triangle



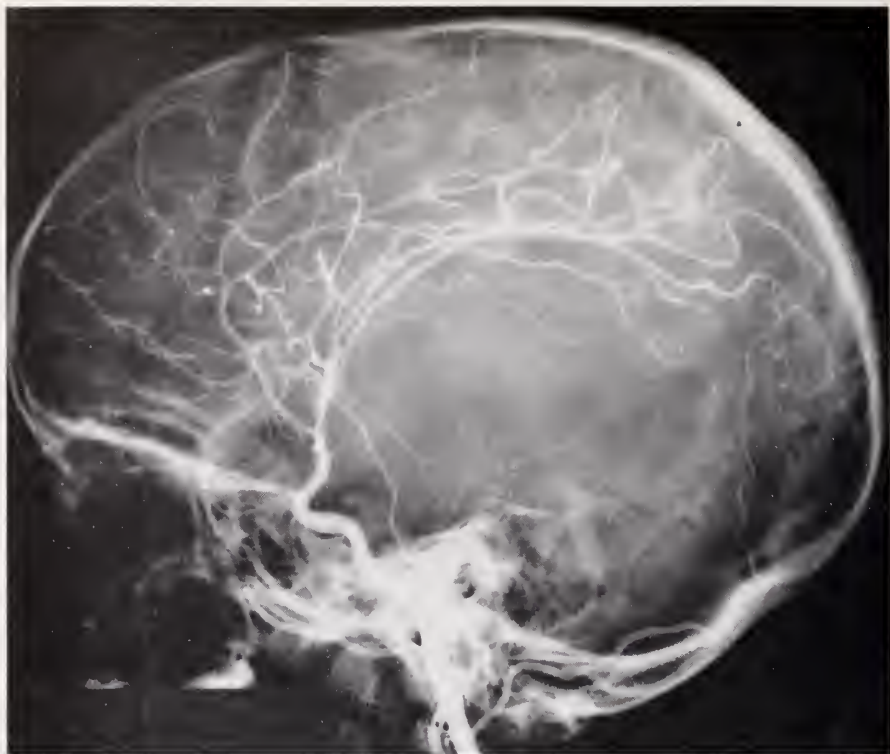


FIG. 29. **Upward Displacement of Sylvian Triangle** (lateral view). The Sylvian Triangle is displaced upwards due to elevation of the middle cerebral artery and its branches by a temporal lobe tumor.

FIG. 30. **Upward Displacement of Sylvian Triangle** (anterior-posterior view). The Sylvian Triangle is displaced upwards by a tumor of the middle cranial fossa.

#### Displacement of the Angiographic Sylvian Triangle

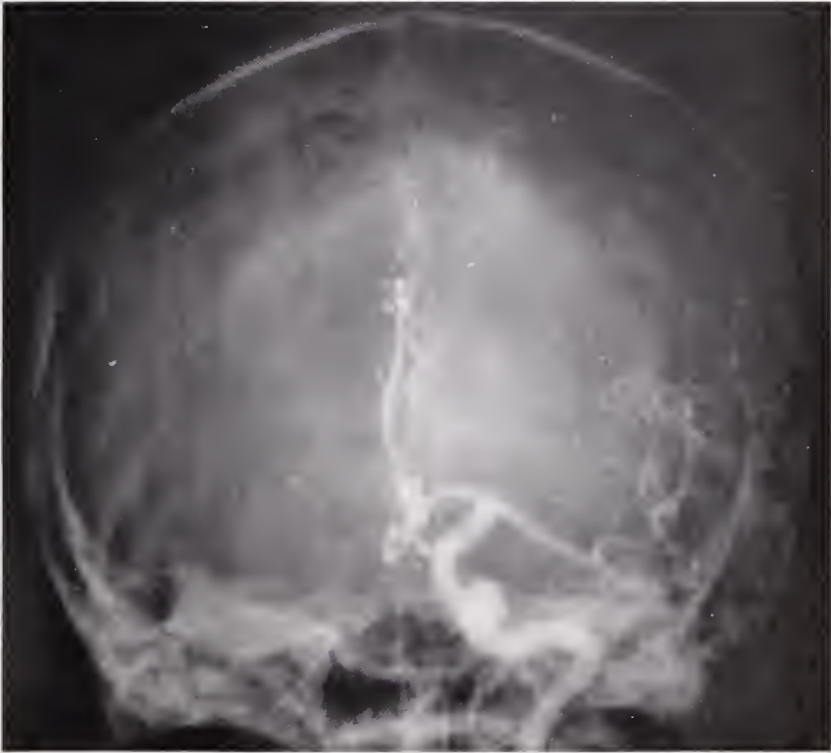


FIG. 31. **Downward Displacement of Sylvian Triangle** (lateral view). The Sylvian Triangle is displaced downward by a parietal lobe mass.

FIG. 32. **Downward Displacement of Sylvian Triangle** (anterior-posterior view). The Sylvian Triangle is displaced downward by a parietal lobe mass.

### Displacement of the Angiographic Sylvian Triangle

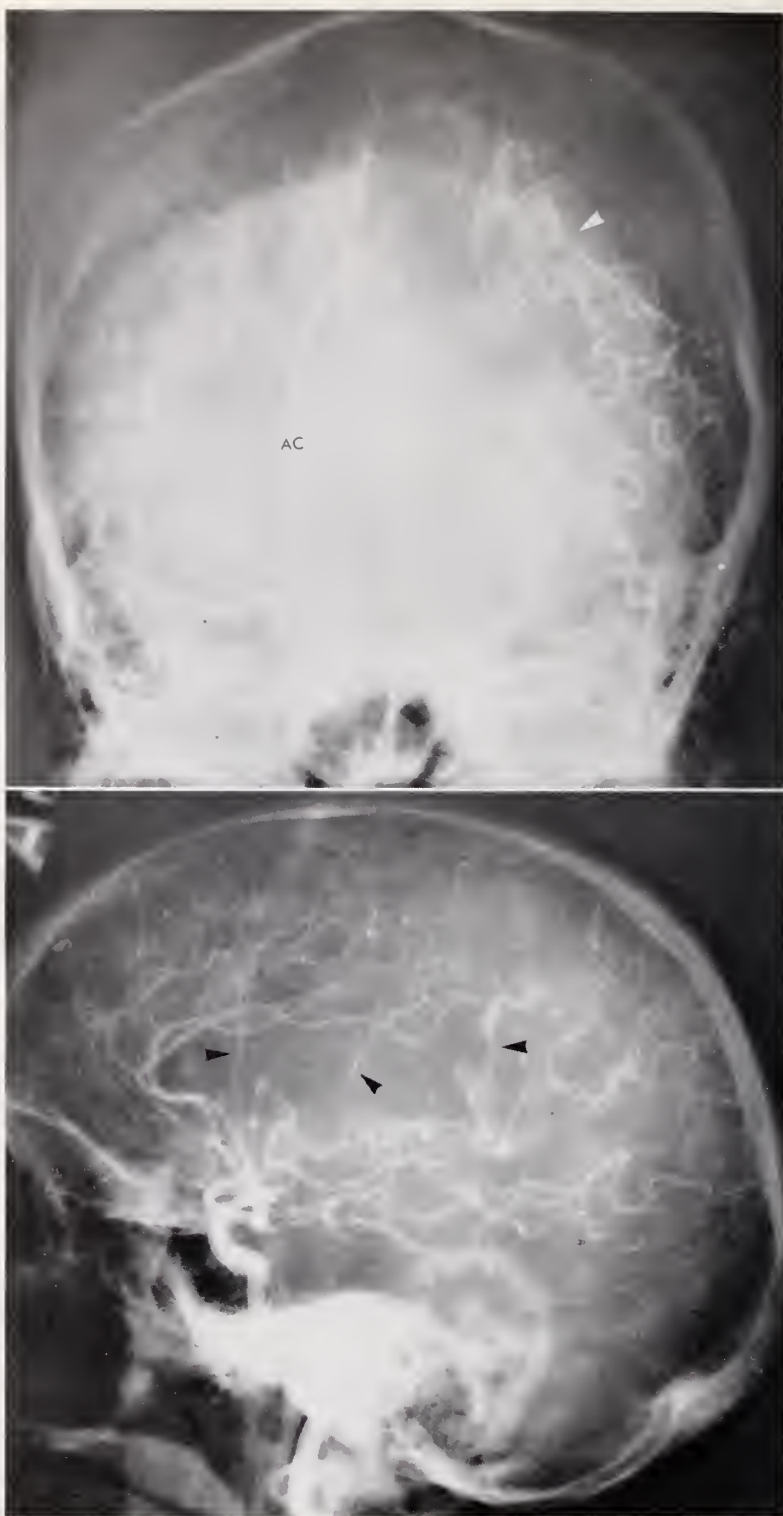
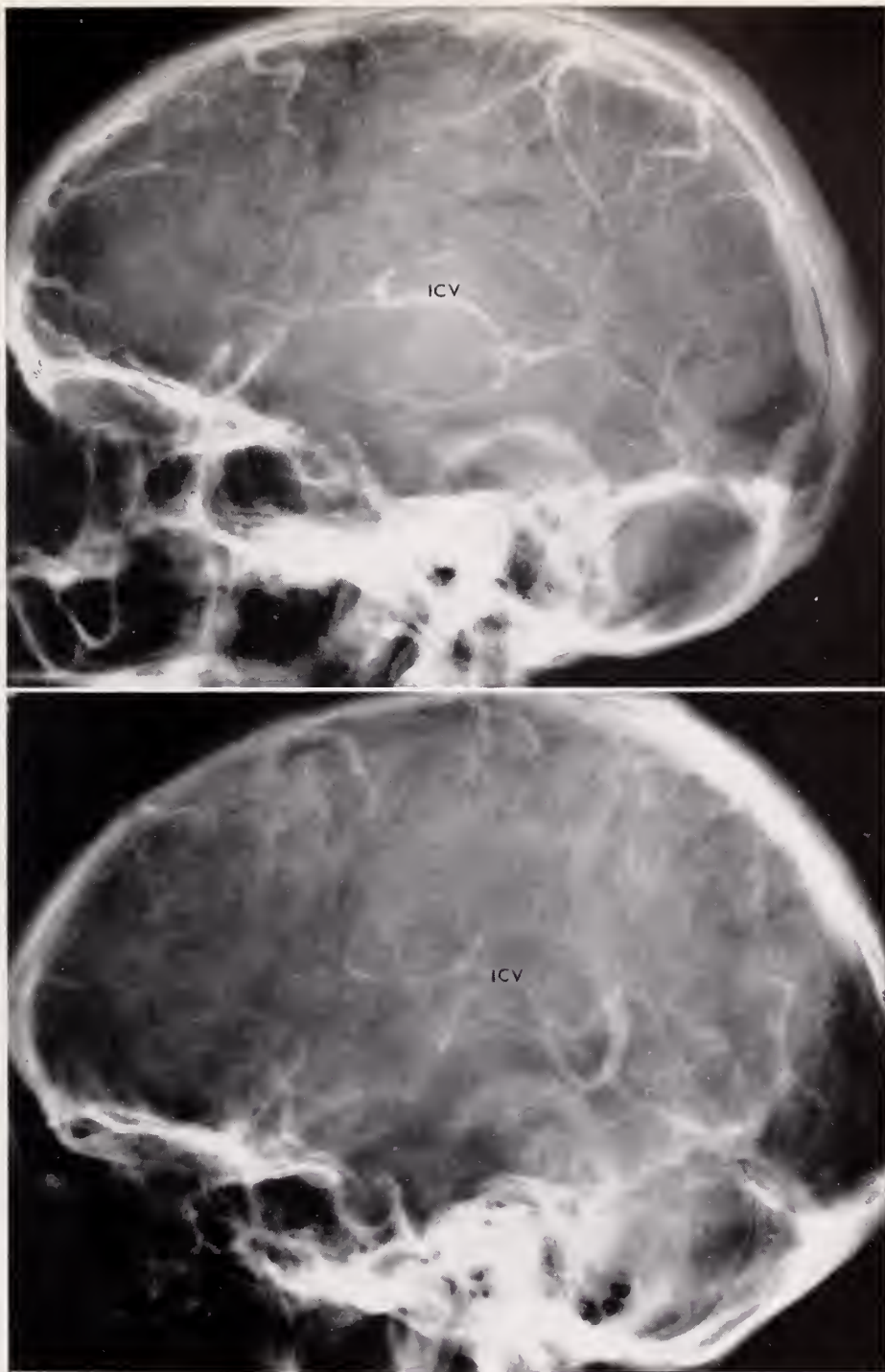


FIG. 33. **Displacement of Vessels by a Subdural Hematoma** (left carotid angiogram, frontal view). The avascular mass displaces and compresses the vessels below it and displaces the anterior cerebral artery (AC) across the midline.

FIG. 34. **Local Deformity of Vessels by a Mass** (right carotid angiogram). The branches of the middle cerebral artery are stretched and bowed due to the presence of a posterior frontal mass.



**FIG. 35. Normal Venous Phase of Right Carotid Angiogram** (lateral view). The internal cerebral vein (ICV) and its branches are shown.

**FIG. 36. Abnormal Venous Phase of Right Carotid Angiogram** (lateral view). Posterior and upward displacement of the internal cerebral vein (ICV) by an anteriorly located mass (meningioma).

**Vessel Displacements**  
(Includes Fig 33 to Fig 36)



## PNEUMOENCEPHALOGRAPHY

Pneumoencephalography is the radiological study of the ventricular system and cerebrospinal fluid pathways of the brain utilizing air as the contrast agent. Although the first of the tests used in neuroradiology, it remains an important diagnostic examination and is frequently the procedure of choice. The air study best demonstrates pathology of the following regions: the posterior fossa, the midline brain structures and the region of the sella turcica. Pneumoencephalography is also preferable to angiography when there are no clinical or electroencephalographic signs indicating which half of the brain is involved or when there is evidence of diffuse brain involvement. Today, cerebral angiography is performed more often for the diagnosis of cerebral disease than pneumoencephalography because it is less traumatic and frequently furnishes definitive etiology. However, both studies may be indicated particularly when the cerebral angiogram is negative or when small or deeply located masses are suspected. In addition, pneumoencephalography furnishes supplemental information regarding the location and size of a mass as well as concomitant changes in the ventricular system. The choice and order of arteriography and/or pneumoencephalography should be determined by the neurologist on the basis of the clinical problem.

### The Procedure

The entire examination is performed in the radiology department under the supervision of a specially trained physician. The patient is premedicated and food withheld. Pneumoencephalographic chairs are now available so that the complete examination can be performed with the patient in this unit. The chair is motor driven and can somersault the patient 360 degrees in either a forward or backward direction.

A lumbar puncture is performed and fluid may be withdrawn for cerebrospinal fluid studies. The presence of increased intracranial pressure is no longer a contraindication for performing an air study nor is the presence of a space-occupying lesion of the cerebrum and/or posterior fossa. Previously, patients with papilledema and/or brain tumors were considered poor risks for pneumoencephalography and consequently ventriculograms were performed. Today, however, using fractional techniques, the threat of tonsillar herniation or sudden decompensation is considerably less.

The patient is positioned with his chin moderately flexed and 15 cc of air instilled slowly. This will provide visualization of the fourth ventricle, aqueduct, and posterior third ventricle (Fig. 37). The examiner looks for displacement, deformities, or lack of filling. The cisterns of the posterior fossa can be visualized by extending the patient's head while 7 cc of air is instilled.



Upon completion of the posterior fossa series, an additional 20 cc of air is instilled for visualization of the lateral ventricles. If the ventricles are of normal size this amount of air will adequately visualize the entire ventricular system. A good guide for estimating whether sufficient air is present is visualization of the shadow of the thalamus in the floor of the body of the ventricle in the erect series.

At this time the spinal needle is removed and the patient placed first with brow up, then later with brow down, thus insuring proper visualization of the entire ventricular system. For visualization of the temporal horns a 360 degree forward somersault is made. The subarachnoid spaces over the cerebral hemispheres can also be visualized. For the investigation of mass lesions in certain areas of the brain, certain modifications of the routine pneumoencephalographic technique is essential. Detection of tumors of the cerebello-pontine angle, such as acoustic neuromas, depends on visualization of the angle cisterns. Mass lesions in and around the region of the sella turcica can be visualized with an unobstructed view of the suprasellar cisterns and anterior recesses of the third ventricle. This is achieved by placing the patient in the supine position with the head fully extended. The entire examination can be performed in less than one hour.

### **Abnormal Radiologic Findings**

The abnormal findings on pneumoencephalography include displacement, deformity, and dilatation of the ventricular system. Displacement of such midline structures as the third ventricle, fourth ventricle, and septum pellucidum are sensitive indicators of the presence or absence of space-occupying lesions of the brain such as neoplasms, hematomas, abscesses and cysts (Figs. 38 and 39). The direction of the displacement indicates the location of the mass. Deformities, signified by changes in the size and shape of the ventricles, indicate the presence and location of a mass (Fig. 40). Local deformities of the ventricles indicate the location of a mass and its shape (Fig. 41). Dilatation of the ventricles occurs with blockage of the cerebrospinal fluid pathways (Fig. 42) and with diffuse loss of brain substance.

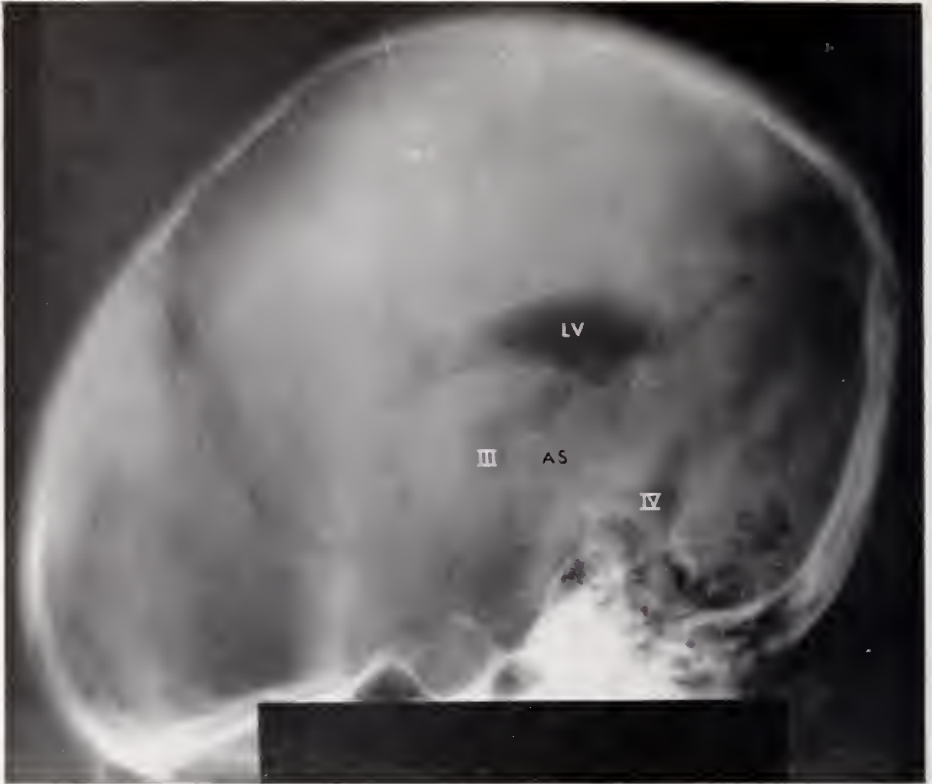


FIG. 37. **Normal Pneumoencephalogram Showing Visualization of the Ventricular System.** The fourth ventricle (IV), aqueduct of Sylvius (AS), third ventricle (III), and lateral ventricles (LV) are visualized.

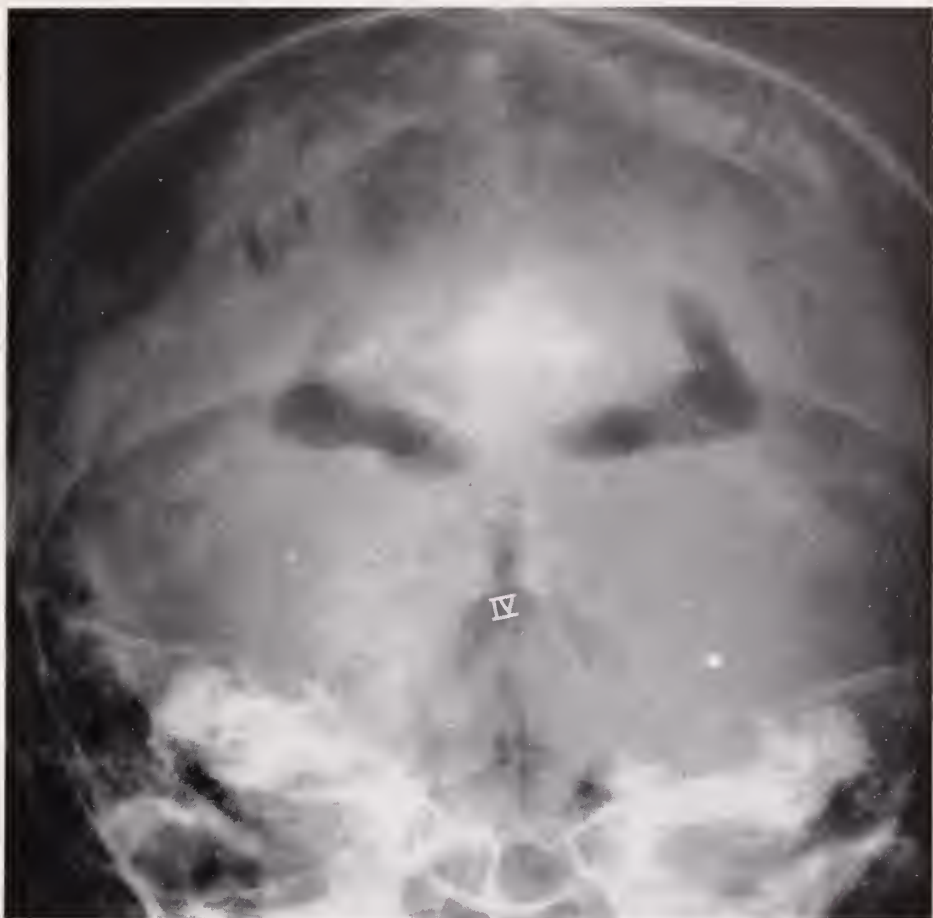


FIG. 38. **Displacement of the Fourth Ventricle.** A tumor within the left cerebellar pontine angle (acoustic neuroma) has displaced the fourth ventricle (IV) and neighboring cistern.

### Displacement of the Ventricular System



FIG. 39. **Midline Displacement of the Ventricular System.** A left subdural hematoma displaces the septum pellucidum and third ventricle (III) across the midline.

FIG. 40. **Depression of the Roof of the Lateral Ventricle.** The roof of the right lateral ventricle is depressed by a mass. There is less subarachnoid air in the region of the tumor.

#### Displacements of the Ventricular System



FIG. 41. **Local Deformity of the Lateral Ventricle.** The air within the body of the lateral ventricle outlines the tumor mass.

FIG. 42. **Dilatation of the Ventricular System.** The fourth ventricle (IV), lateral ventricle (LV), and occipital horn (OH) are markedly enlarged.

#### Deformity and Dilatation of the Ventricular System



## MYLEOGRAPHY

Myelography is the radiographic examination of the contents of the spinal canal. It enables the neurologist to study and evaluate those disorders referable to the spinal cord, nerve roots, and bony vertebral canal. It is a valuable diagnostic test and a useful aid in determining the type and course of treatment. Although there remains a sizeable gap in our understanding of disease states affecting the spinal cord and nerves it is incumbent upon the physician to utilize all resources available to him. Myelography is an essential part in the complete neurological evaluation of a patient when spinal cord or root problems are present.

### The Procedure

A myelogram can be performed so that either the entire region or a specific region of the spinal canal is studied. The examination is performed by a physician in the radiology department in a room provided with a fluoroscopic tilt table and preferably equipped for television viewing. The patient is usually premedicated with a mild sedative. In cases where myelography is contemplated the routine lumbar puncture may be postponed until the puncture for the myelogram is made. At that time manometrics should be done, and spinal fluid specimens obtained.

Approximately three cc of contrast media is instilled and a Polaroid x-ray film is taken to see if the media is flowing within the subarachnoid space. Usually a total of 15 to 18 cc of contrast media (Pantopaque) is sufficient for a myelogram.

Under fluoroscopic control, the physician can see the movement of the contrast media up and down the spinal cord; and, when indicated, x-rays are taken. The patient is placed in the prone position with a harness so as to allow for tilting of the x-ray table. Occasionally, during the examination the spinal needle is removed and the patient is repositioned in the supine position for viewing of the posterior portion of the canal and foramen magnum. Otherwise, the needle is kept in place until the termination of the examination, so that the Pantopaque can be removed and, if desired, medication such as Depo-Medrol instilled intrathecally. It is essential that the x-ray films include all of the proper views as the success of a complete and diagnostic myelogram is dependent upon adequate visualization of the suspected area of pathology. Upon completion of the examination the patient may resume normal activity the following day. Occasionally, low back and/or radicular pain may ensue for a brief period. Isolated cases of post myelographic arachnoiditis have occurred, but fortunately the incidence is very low, and even lower when care is exercised in the performance of the examination.

## Indications

Myelography is indicated for any acute, chronic, or sub-acute condition in which the site of pathology is referable to the spinal cord, roots, nerves, or the bony spinal canal. The conditions and disease processes involved are legion and reference will be made only to the more common disorders.

Discogenic disease, with its complex and manifest clinical picture, is best evaluated by myelography. The choice of therapy, conservative or surgical, and the course of the condition can be best evaluated when a myelogram is performed. Not uncommonly, a tumor presents clinically as a herniated disc. This differentiation can be made easier with a myelogram. In other instances, slowly progressive symptoms suggesting a tumor may actually be an extruded disc. This is particularly common in the cauda equina region. Although the lumbosacral and cervical spine are the most common sites for disc disease and degenerative changes, the thoracic spine occasionally is the site of such disturbance. The presence of radicular pain, motor and/or sensory loss in any limb may be a manifestation of arthritic involvement of the spine. When it is sufficiently advanced, there may be accompanying spinal cord involvement. Myelography is essential for the evaluation of the site, extent and nature of the spondylotic process. Cervical spondylosis has often been found to simulate the clinical picture of multiple sclerosis, so-called primary lateral sclerosis, and amyotrophic lateral sclerosis. Bizarre symptomatology such as impotence, sphincter disturbance, and loss of muscle bulk are often manifestations of arthritic involvement of the spine.

Myelography is essential for the study of tumors of the spinal canal. Neoplasms can be present within the bony canal, the covering or meninges of the spinal cord, or in the spinal cord itself. Differentiation can best be made by myelography and is essential in determining the exact site and nature of the tumor. Such information will enable the neurologist to decide whether radiotherapy, surgery, or conservative management is required.

## Abnormal Radiologic Findings

Mass lesions arising from the spinal cord such as gliomas are recognized on myelography by the widening of the spinal cord shadow and the narrowing of the column of Pantopaque (Fig. 43). Mass lesions arising from the spinal coverings such as meningiomas and neurofibromas show characteristic intradural deformities of the Pantopaque column. Since they arise from the meninges they cause widening of the Pantopaque column and concurrent displacement of the spinal cord (Figs. 44 and 45). Tumors of the bony vertebral canal or those present within the spinal canal itself cause a characteristic extradural deformity. These masses compress the spinal coverings and cause both narrowing and displacement of the Pantopaque column. Herniated discs produce such extradural defects at the intervertebral disc space (Fig. 46).

In cases of acute or chronic spinal cord compression myelography will detect whether or not there is a partial or complete block to the flow of cerebrospinal fluid. The effectiveness of a decompression whether surgical or by radiotherapy can be subsequently evaluated on repeat myelography. Less common lesions such as arteriovenous malformations, cysts and syrinx are best demonstrated on myelography.

### **Myelencephalography and Special Techniques**

As a further extension of the versatility of myelography, the structures within the posterior fossa have been studied with Pantopaque. The myelencephalogram or MEG is performed in the same manner as a routine myelogram except that the patient is placed in the supine position and the table tilted so as to enable proper outlining of the 4th ventricle, aqueduct, and posterior third ventricle with contrast media. This technique is performed when other contrast examinations have furnished insufficient information concerning space-occupying lesions in the posterior fossa. A modification of this examination is the fossagram in which the basilar cisterns of the brainstem are outlined with Pantopaque. This is of great aid in the diagnosis of acoustic nerve tumors.

In addition to the use of radiopaque contrast media, air is used to outline the spinal cord in myelography. However, its use is limited to only certain areas of study. The use of video viewing and simultaneous tape recording of myelograms has greatly facilitated the speed and efficacy of the examination and is an example of the many advances that have recently been made.

### *Acknowledgment*

We should like to thank Drs. Bernard S. Wolf, Morris B. Bender and Yun Peng Huang for permission to use selected x-ray films.



FIG. 43. **Intramedullary Spinal Cord Mass** (myelogram, frontal view). Widening of the cord shadow and narrowing of the column of contrast media by a glioblastoma of the upper cervical cord.



FIG. 44. **Extramedullary Intradural Mass** (myelogram, lateral view). The column of contrast media is blocked, widened, and the cord shadow displaced (arrow) by a thoracic meningioma.

### Intra and Extramedullary Spinal Masses



FIG. 45. **Extradural Intradural Mass** (myelogram, frontal view). The smooth, dome shaped outline of a mass within the lower lumbar intradural space is outlined by the column of contrast material. The column is



thinned around it and widened (arrows).

FIG. 46. **Extradural Mass** (myelogram, oblique view). The column of contrast media is indented at L5-S1 by a herniated disc.

#### Intra and Extradural Spinal Masses



## In Memoriam

JOHN H. GARLOCK

1896-1965

June 6, 1965, while working on the last chapter of a book on gastrointestinal surgery, Dr. John H. Garlock suffered a vascular catastrophe which was rapidly fatal.

John Garlock was born in New York City August 29, 1896. He was an excellent student, completing the course at Townsend Harris High School in three years. He graduated with highest honors in his class including the prizes in Latin, Greek, German, and Zoology and he was Valedictorian of his class. Following premedical preparation at the College of the City of New York, he attended Columbia University and then the College of Physicians and Surgeons. He was elected to membership in the Alpha Omega Alpha honorary medical society and graduated in 1919 with the degrees of Bachelor of Arts and Doctor of Medicine.

He then won the coveted appointment to the Surgical Service of Dr. Eugene Pool at New York Hospital. Under the tutelage of this strict taskmaster and well-known surgeon, Dr. Garlock received his fundamental surgical training and was exposed as well to exercises calculated to develop high standards of character and personal behavior. He idolized his chief, and always strove to follow his precepts of concise thinking, resolution of purpose, personal integrity and devotion to the ideal of professional perfection.

Two years after completing his training as House Surgeon he was appointed Assistant Visiting Surgeon at New York Hospital in 1923, Instructor in Surgery at Columbia University in 1925, and shortly thereafter Assistant Clinical Professor of Surgery at Cornell University Medical College. During these early years he was concerned chiefly with general surgery, traumatic surgery, plastic surgery, thyroid surgery, and the surgery of the hand.

In 1933 Dr. Garlock came to The Mount Sinai Hospital. He advanced rapidly through the Attending Staff ranks. Three and one-half years later he was appointed Attending Surgeon and Chief of the Surgical Service. His was the opportunity to follow in the Mount Sinai tradition of gastrointestinal surgery. He gained extensive experience in the problems relating to the surgical treatment of peptic ulcer, gastric cancer, inflammatory diseases of the small and large bowel and surgery of the biliary tract, and contributed significantly to the literature in these fields.

In 1937 the esophagus was still in the "No Man's Land" of surgery. Dr. Garlock undertook the challenge of the surgical attack on cancer of this organ and of the gastric cardia. It was not long before his work in developing



JOHN H. GARLOCK, M.D.  
1896-1965

successful new techniques won him world-wide recognition as a pioneer contributor in this hitherto inaccessible area. During ensuing years his interest in the esophagus led him to gain extensive experience in the therapy of other esophageal lesions as well including hiatus hernia, esophagitis, stricture, diverticula and achalasia.

Dr. Garlock's contributions to the surgical literature number upwards of one hundred sixty-five publications including a monograph on the surgery of the hand and chapters on esophageal and intestinal surgery. His magnum opus, a book setting forth his extensive personal experience in the surgery of the alimentary tract, is to be published soon.

Dr. Garlock was considered not only a master surgeon in terms of technical grace and facility in the operating room, but a good practitioner as well. His diagnostic clinical judgment and acumen were highly developed. He was also an excellent consultant. He was fond of saying that a day was wasted in which he did not learn something new. Severely critical in his own work, he consistently refused to follow unproven facts in surgery, yet he never hesitated to alter his personal concepts and techniques in accordance with newly developed sound physiological principles.

Dr. Garlock has the unique distinction of being a founding member of the American Board of Surgery, the American Board of Thoracic Surgery, and the American Board of Plastic Surgery. He was also a member of the American Gastroenterological Association and the New York Surgical Society, and a Fellow of the American College of Surgeons and the New York Academy of Medicine. Other honors included an invitation to give the John Hunter Luck Lecture at the Royal College of Surgeons in London in 1947 and to address the French Academy of Surgery a few days later to present his work in the then new surgical treatment of cancer of the esophagus and gastric cardia. For many years he was Clinical Professor of Surgery at Columbia University. He was also a Chevalier of the French Legion of Honor and a honorary member of the Brazilian College of Surgeons, the Surgical College of Chile and the Japanese Surgical Association.

His intense activity in surgery notwithstanding, Dr. Garlock found time to develop interests in other fields. He served on various committees of the New York County Medical Society and served a term as its President. He was well known for his interest in music and was an accomplished pianist. In addition, he sponsored aid to indigent musicians and played an important part in launching the career of a well-known concert violinist. He also became adept as an amateur painter in oils and watercolors.

Dr. Garlock was for many years interested in the Hebrew University in Israel. He was a Trustee of the American Friends of the Hebrew University, and as Chairman of the American Jewish Physicians Committee he directed fund raising activities for several years. In his honor, an operating room in the Hadassah Hospital bears his name.

Although frequently gruff in manner, John Garlock was loved and respected

by his patients, house staff and nursing staff, and by the many disciples who trained under his auspices. He was not a "spoon-feeding" teacher; rather, he believed that a surgeon should learn by example, by observation, and by self application in the development of techniques and habits of logical thinking and study. It is indeed noteworthy that many of the men who worked with Dr. Garlock have themselves achieved positions of rank and responsibility. Their accomplishments afforded him much personal satisfaction and pleasure.

This untimely loss has left a great void among us. John Garlock is sorely missed. His achievements not only greatly enriched the century old tradition of Mount Sinai, but also earned him many honors in this country and abroad. It is certain that his memory shall long endure.

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## External Scanning of Internal Beta-Emitters

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Scanning for the detection of radioactive material within the human body usually depends upon the emission of gamma rays from the radioactive isotope. The distribution in the body of the gamma-emitting isotope can be determined by moving the detector (scintillation crystal) over the surface of the portion of the body to be examined, the process of scanning. The record made of the detected gamma rays constitutes a map of the distribution of the isotope within the body. Gamma rays of clinically useful isotopes are sufficiently penetrative to emerge from the patient and to be detected and recorded by the scanner.

The detection of internally deposited isotopes which emit beta particles (electrons), however, has not been clinically feasible. Beta particles, less penetrative than gamma rays, are absorbed by a few millimeters of tissue. Hence internally administered beta-emitting isotopes have not been considered suitable for detection by scanning. However, our recent observations indicate practical external detection of internal beta emitters in the abdomen.

Beta particles (electrons) have finite, short ranges in tissue, their penetration depending on their energy. As an example, phosphorus-32 is a pure beta-emitter. The maximal energy of its beta particle is 1.7 mev with a range in tissue of 9 mm. Thus, the energy from the deeply imbedded  $P^{32}$  in the body would ostensibly be absorbed completely. Localizing this beta-emitting isotope by measuring the beta particles themselves would involve placing the detector inside or very close to the tissue containing the  $P^{32}$ . But beta particles traversing through tissue lose some of their energy as bremsstrahlung, secondary x-rays like those generated in an x-ray tube. The efficiency of this conversion of energy to bremsstrahlung is low, especially in tissue which is of relatively low atomic number. Because of this known low efficiency little attempt has been made to detect internal beta-emitting isotopes with scintillation crystal scanning equipment. Our preliminary attempt to detect and scan yttrium-90 and phosphorus-32 within the abdomen resulted in scans which were surprisingly good and which provided clinically useful data.

### CASE REPORTS

#### *Case 1*

A 53 year old housewife has had attacks of flushes, cramps, nausea, diarrhea, vomiting, prostration and hypotension due to abdominal carcinoid tumor

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for the past 6 years. Needle aspiration biopsy of the liver established the diagnosis in 1961. Recent abdominal operation to catheterize the hepatic artery showed tumor involving the liver, but the exact site of the primary tumor was not determined. During these past 6 years of her illness she has been treated with chemotherapy and external radiation. At one time 5 fluorouracil (5 FU) was injected into the hepatic artery, and later the patient had a constant drip of 5 fluorodeoxyuridine (5 FUDR) in the indwelling arterial catheter for 5 months. For 9 months cytoxan was given by mouth. A large mass in the liver was also treated with cobalt teletherapy, an exposure dose of 3000 rad in 3 weeks through a 12 by 12 cm field. Symptomatically, the patient had responded favorably to these therapeutic methods, and the serum serotonin levels dropped temporarily with each series of treatments. When her symptoms and signs returned she was readmitted to The Mount Sinai Hospital for internal irradiation of the liver with yttrium-90. On admission the patient was having frequent carcinoid attacks. The liver was large, its lower border was notched and nodular. The estimated weight of the liver was 2500 gm, and its lower edge was 5 cm below the right costal margin. Under fluoroscopic control a catheter was passed percutaneously through the left axillary artery into the hepatic artery. Some temporary technical difficulty was met in passing this catheter because of the distorted anatomy associated with the tumor and with previous abdominal operations. When an arteriogram verified the position of the catheter in the hepatic artery (Fig. 1), 50 mc of  $Y^{90}$  was injected into the hepatic artery, presumably in the distribution indicated in the arteriogram. The  $Y^{90}$  was bound firmly to plastic spheres 15 microns in diameter and suspended in dextran (3M Brand Yttrium Microspheres). To determine whether the  $Y^{90}$  was in the liver, a scan was made 2 days after the injection of the isotope. The spectrometer was set to measure bremsstrahlung between 75 and 300 kv, and the maximal counts per minute were 28,000 (Picker Color Magnascanner III, 3 in x 2 in NaI crystal). The resultant color scan (Fig. 2) shows the activity of the  $Y^{90}$  to coincide well with the distribution of the vessels as seen in the corresponding arteriogram (Fig. 1).

### *Case 2*

A 40 year old woman had carcinoma of the ovary and ascites for one year. Her disease had been under control by chemotherapy, hormone (androgen) therapy and occasional paracentesis. The present admission to The Mount Sinai Hospital was for another abdominal tap and the instillation of  $P^{32}$  into the abdomen to suppress the formation of fluid. A plastic paracentesis tube was inserted into the peritoneal cavity in the right lower quadrant of the abdomen and 5 liters of fluid drained off into the bedside bottle in 48 hours. The tube was obstructed; no solution could be injected into it. The abdomen was flat and "dry." Through a 14-T needle, another plastic tube was inserted into the peritoneal cavity on the left; the exact placement of this tube was uncertain because of the distorting masses of tumor. Chronic phosphate ( $P^{32}$ ) colloid, 5 mc in 5 ml of solution, was injected into the peritoneal cavity and 50 cc of

sterile saline injected to follow. The patient was then instructed to change positions in bed to attempt spreading of the radioactivity through the abdomen. Two days later a scan of the anterior abdomen was made to determine the distribution of the radioactive colloid in the abdomen.

The spectrometer window was set between 75 and 300 kv, and the maximal

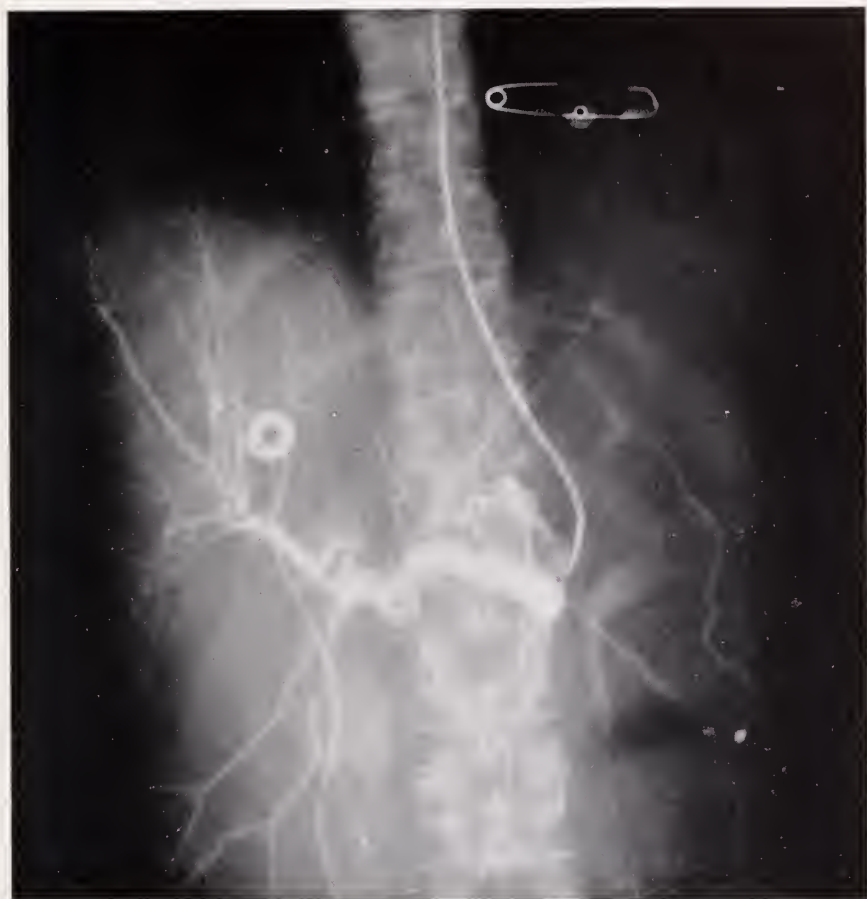


FIG. 1. Injection of contrast material through the catheter confirms its position in the common hepatic artery. The catheter was passed percutaneously through the left axillary artery and advanced into the celiac artery until its tip was distal to the origins of the splenic and gastric vessels.

counts were 10,000 counts per minute. In the color scan (Fig. 3), the activity is distributed throughout the abdomen. Although the distribution is not even, no indication of significant loculation is demonstrated.

#### DISCUSSION

The ability to determine the distribution in the body of a beta-emitting isotope is of clinical value.  $Y^{90}$  microspheres are now being used for intra-

vascular injection in the attempt to confine irradiation to a single organ. The exact localization of the microspheres has been studied in the past by making test microspheres containing gamma-emitters and injecting these in tracer

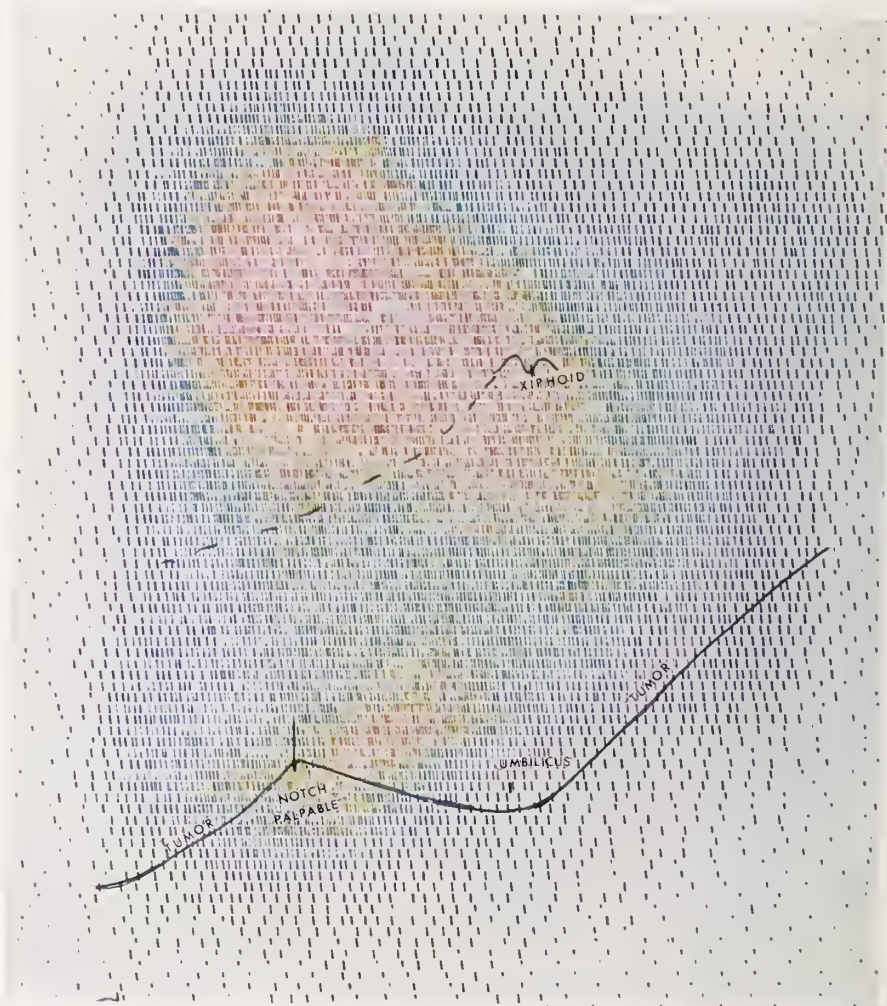


Fig. 2. Color scan of the liver of patient with carcinoid tumor (Case 1). The  $Y^{90}$  microspheres were injected directly into the common hepatic artery. The highest intensity of bremsstrahlung is in red, indicating that the microspheres are concentrated in the distribution of the intra-arterial contrast material in Fig. 1. The lower solid line represents the palpable edge of the enlarged liver. The dotted line above it is the costal margin with the xiphoid to show the midline.

amounts for scanning while the beta-emitting isotope simultaneously carries the biologically effective radiation. Thus Kim and associates (2) have used scandium-46, a strong gamma-emitter, and Ariel (3) has used ytterbium-169 to obtain scans of the distribution of microspheres. With the use of the beta-emitting therapeutic isotope  $Y^{90}$  such tracer doses of gamma-emitting



isotopes are unnecessary since the  $Y^{90}$  provides sufficient bremsstrahlung to make the scans.

A scan of other organs may help to determine whether intra-arterially injected

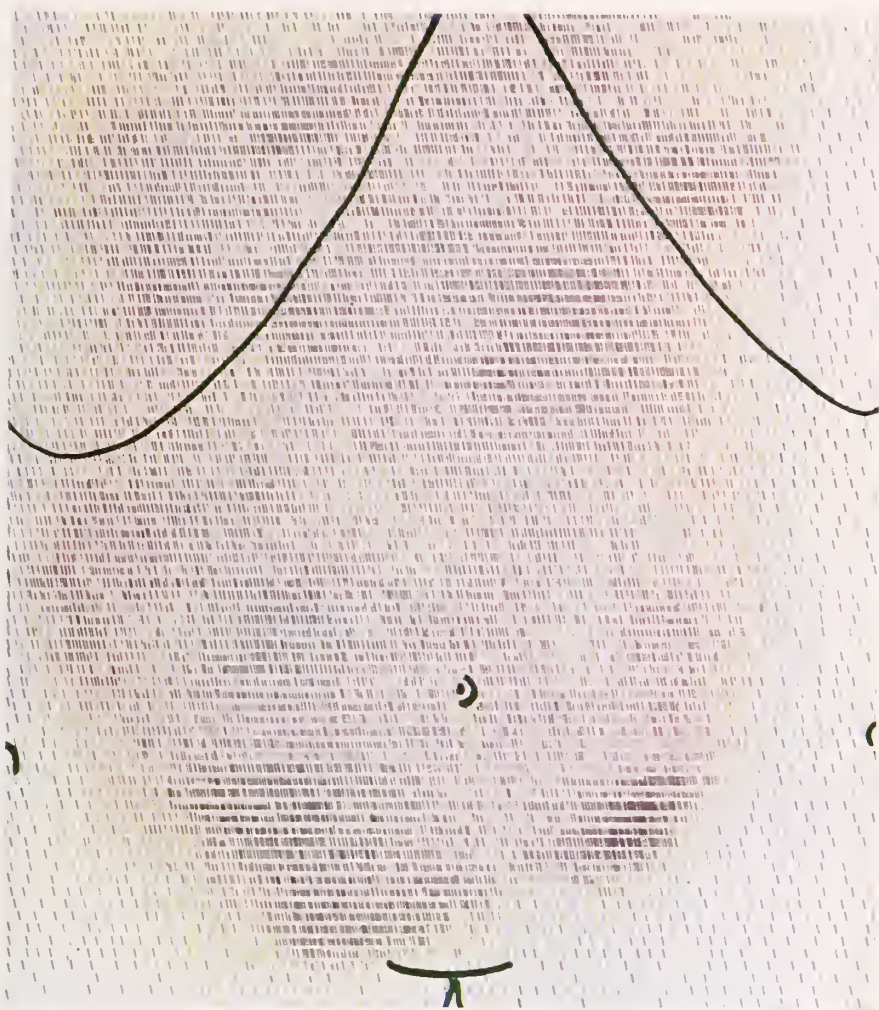


FIG. 3. Color scan of the abdomen (Case 2) after the intraperitoneal injection of chromic phosphate ( $P^{32}$ ) colloid. The activity is distributed diffusely throughout the abdomen; no significant "hot spot" is demonstrated. Umbilicus, costal margins, iliac spines and pubis are drawn on the scan.

$Y^{90}$  microspheres have been injected only into the desired region. For example, if there is spill-over from the hepatic artery into the celiac axis and aorta, activity might be picked up in the feet or pelvis. A scan of the pelvis and feet of the patient described in Case 1 showed no discernible activity in these regions.

Now that percutaneous intra-arterial catheterization of many vessels is a

clinically practical procedure, the ability to scan beta-emitting isotopes in the distribution of these vessels should be useful in showing the exact distribution of intra-arterially injected isotopes.

For about 20 years radioactive isotopes (mainly gold-198 and  $P^{32}$ ) have been used for the treatment of pleural effusions and ascites due to cancer.  $Au^{198}$  in the form of a colloid of gold chloride was favored for such therapy in The Mount Sinai Hospital because its 400 kv gamma ray enabled us to follow its distribution in the pleura or peritoneal cavity by external counting or even by actual radioautograph of the patient on a large x-ray film (4). The scan (Fig. 3) of the patient (Case 2) demonstrates that we can locate  $P^{32}$  without exposing personnel to the gamma rays from radioactive gold and without giving the patient an unnecessarily higher integral dose from the gold. The scans of the bremsstrahlung from  $P^{32}$  should demonstrate the advantage of this isotope over  $Au^{198}$  where isotopes are indicated in the treatment of intractable effusions.

Conversion of beta radiation to bremsstrahlung is a very inefficient process (5). The ionizing events detected from the bremsstrahlung from  $P^{32}$  in tissue represent only a small fraction of the ionizing events detected from the beta particle emission. Despite the inefficiency of the conversion of beta radiation to bremsstrahlung, therapeutic doses of isotopes are so high that the counting of bremsstrahlung is feasible. Diagnostic test or tracer doses may not yield sufficient bremsstrahlung for practical counting. In our preliminary scans the spectrometer was set to exclude energies below 75 and above 300 kv, but more efficient settings and factors may result from further experience.

#### SUMMARY

Available scanning devices are able to detect and record the distribution of beta particle emitting radioisotopes within the body. Scans of  $Y^{90}$  injected intra-arterially and scans of  $P^{32}$  injected intraperitoneally are practical clinical applications.

#### REFERENCES

1. Heidelberg, J. G., Sirota, P. G., Dewey, W. C., and Rose, R. G.: Determination of the Distribution of  $P^{32}$  in Phantoms and in Patients by Detection of Bremsstrahlung Radiation with a Scintiscanner. *Am. J. Roentgenol.*, **90**: 325, 1963.
2. Kim, Y. S., LaFave, J. W., and MacLean, L. D.: The Use of Radiating Microspheres in the Treatment of Experimental and Human Malignancy. *Surgery*, **52**: 220, 1962.
3. Ariel, I.: Treatment of Inoperable Primary Pancreatic and Liver Cancer by the Intra-Arterial Administration of Radioactive Isotopes ( $Y^{90}$  Radiating Microspheres). *Ann. Surg.*, **162**: 267, 1965.
4. Simon, N., Abrams, J., Khilnani, M., Margolin, H. N., Gurman, S. I., Eliasoph, J., and Mayer, J.: The Use of Radioactive Gold in the Treatment of Effusions Due to Cancer. *J. Mt. Sinai Hosp.*, **20**: 237, 1953.
5. Feitelberg, S. and Loevinger, R.: Using Bremsstrahlung Detection by a Scintillator for Simplified Beta Counting. *Nuclconics*, **13**: 42, 1955.

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# Massive Hemorrhage in Diverticular Disease of the Colon

ROBERT PARADNY, M.D., AND ALLAN E. KARK, M.D.

As recently as ten years ago, opinion was expressed that bleeding rarely, if ever, occurred in diverticular disease. At a joint meeting of The American College of Surgeons and The Royal College of Surgeons of England (1) in 1954 all members of a panel stated that they had no experience with massive bleeding from diverticulitis of the colon. Yet Rives and Emmett (3) in the same year concluded from their study of patients with melena, at Charity Hospital in New Orleans, that diverticular disease of the colon was the most common cause of massive bleeding from the lower gastrointestinal tract. Noer (2) in 1955 reviewed 28 series of cases reported between 1934 and 1954 and found that bleeding occurred in from 3 to 47 per cent of cases, most reporting an incidence of between 10 to 30 per cent. Severe hemorrhage occurred in 2 to 6 per cent of cases.

Six cases admitted recently to the surgical service of The Mount Sinai Hospital with massive hemorrhage from diverticular disease are presented. In four cases severe hemorrhage did not abate and emergency colonic resection was required. Two patients stopped bleeding and then had elective resection.

## CASE NO. 1

A 67 year old achondroplastic Negro man was admitted to The Mount Sinai Hospital for the first time March 28, 1963 with a six-hour history of rectal bleeding. In 1936 he had passed red blood per rectum and had had a hemorrhoidectomy at another hospital. There was no further bleeding until 1956 when he was admitted elsewhere with bright red rectal bleeding. An investigation was said to reveal "pockets" in the intestine.

At 10 p.m. on March 28, 1963 he began passing many large bloody stools with clots. He appeared in the emergency room and was admitted to the hospital. He had no other gastrointestinal complaints.

Physical examination revealed a short stocky man with a long torso and stunted extremities typical of achondroplasia. His blood pressure was 100/70 and pulse 100. The abdomen was soft, non-tender, and obese. No organs or masses were felt. Rectal examination was negative except for dark red blood and clots. The hematocrit was 25. Sigmoidoscopic examination was possible only to 9 cm, where marked angulation prevented further penetration. The mucosa was normal and the rectum was filled with dark red blood and clots.

Five hundred ml of whole blood was started but discontinued after 300 ml because of shaking chill. His vital signs were stable until 2 p.m. on March 29, 1963 when his blood pressure fell and further transfusion was necessary. By 9 p.m. bleeding became profuse and continuous and required rapid replacement. An emergency barium enema revealed many diverticula throughout the colon (Fig. 1a). The patient was taken to the operating room having received 9000 ml of blood from time of admission to operation.

At operation, the entire colon was filled with blood, the left colon being most markedly distended. There were multiple diverticula involving all of the colon. Two colotomies were performed, one in the sigmoid and one in the distal transverse colon. After aspiration of colonic contents through these colotomies, there was reaccumulation and outpouring of blood from the sigmoid colotomy but none from the transverse colon colotomy. A left hemicolectomy was then



FIG. 1a. Preoperative barium enema examination in Case No. 1.

performed with anastomosis of midtransverse colon to the lower sigmoid just above the peritoneal reflection.

Postoperatively the patient developed a wound infection and a fecal fistula, but after prolonged hospitalization these healed.

Pathology report: Segment of colon showing diverticulosis. No ulceration or vascular change of the mucosa was found (Fig. 1b).

The patient was last seen in follow up clinic May 1965, at which time he had no complaints referable to the gastrointestinal tract. There had been no further bleeding (Fig. 1c).

## CASE NO. 2

A 72 year old elevator operator was admitted May 23, 1963 shortly after he passed a large bloody stool and fainted. He was pale but his vital signs were stable. Hemoglobin on admission was 8.5 gm per cent. Five hundred ml whole blood was given. Sigmoidoscopy revealed only blood and clots in the rectum coming from above 25 cm. For 12 hours his vital signs remained stable, and he passed only small amounts of red blood, but then he began to bleed massively. Blood was administered rapidly and a barium enema was performed revealing numerous diverticula throughout the colon. In addition,

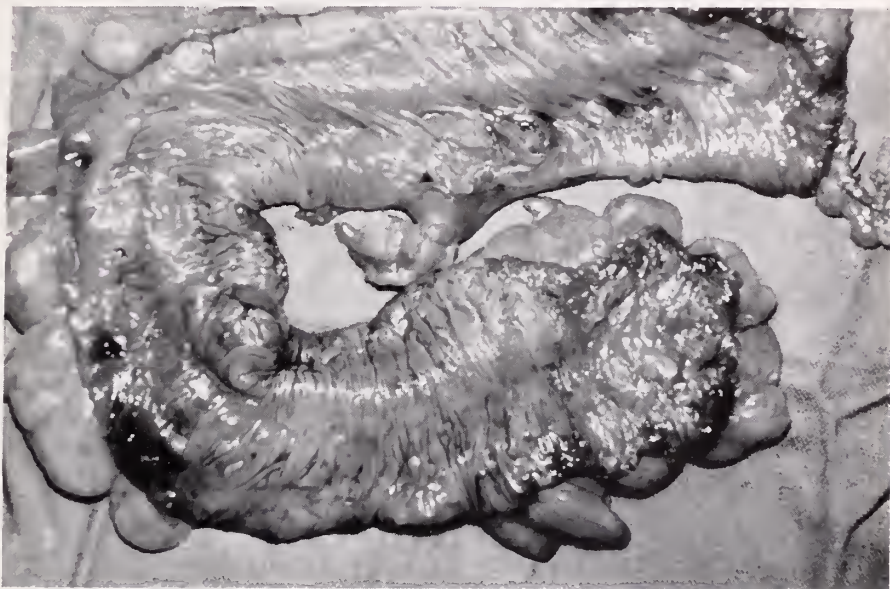


Fig. 1b. Left colon resected as an emergency in Case No. 1.

there was a mass in the transverse colon close to the hepatic flexure (Fig. 2a). He was taken to the operating room and a right hemicolectomy was performed after it was demonstrated, with a clamp across the midtransverse colon, that the bleeding was from the right side. The mass in the right transverse colon was a giant diverticulum containing feces (Fig. 2b).

Pathology report: Diverticulosis of colon and chronic diverticulitis of the transverse colon showing a large diverticulum.

The patient was last seen in follow up clinic September 1963 and was without complaints.

## CASE NO. 3

A 76 year old woman was admitted to the medical service of The Mount Sinai Hospital on the evening of December 30, 1963 with rectal bleeding of 12

hours duration. She had been on the medical service twice in 1957 with episodes of red and tarry stools and hemoglobin levels of 4.7 and 9.0 gm per cent.

Investigation on both occasions (including upper gastrointestinal series, small intestinal x-rays, barium enema, sigmoidoscopy and string tests) showed only extensive diverticulosis of the colon extending from the right transverse colon to the lower sigmoid.



FIG. 1c. Postoperative barium enema examination in Case No. 1.

The patient had no rectal bleeding and no complaints referable to the gastrointestinal tract between 1957 and the morning of admission when she began to pass red blood.

Physical examination revealed an elderly obese woman in no acute distress. Her blood pressure was 120/70 and pulse 96. The abdomen was slightly distended and loops of bowel were palpable but there were no masses felt. Rectal examination revealed currant jelly stool. Hematoerit on admission was 32 per cent. It fell to 20 per cent by the next morning and one unit of blood and two units of packed cells were given. The patient passed 2 large bloody stools



during the late afternoon and 2 more units of whole blood were given. By 10 p.m. she was passing bloody stools almost continuously, and at midnight, the patient was taken to the operating room with a hematocrit of 32 per cent having received a total of 7500 ml of blood.

At operation, multiple diverticula were noted extending from the right transverse colon to the rectosigmoid. Resection of the left colon with anastomo-



FIG. 2a. Preoperative barium enema in Case No. 2 revealing diffuse involvement of colon with diverticula.

sis of the right transverse colon to the lower sigmoid 4 cm above the peritoneal reflection was carried out.

Pathology report: Segment of colon showing diverticulosis. An occasional diverticulum showed focal mild chronic non-specific inflammation.

When last seen in the follow up clinic January 1965 the patient had no complaints and there was no recurrence of bleeding.

#### CASE NO. 4

A 65 year old woman was admitted July 31, 1962 with severe rectal bleeding and weakness of 12 hours duration. She had had many previous admissions



to the medical and surgical wards for diabetes mellitus, hypertension, arteriosclerotic heart disease, chronic cholecystitis and two myocardial infarctions in 1954 and 1956. In 1956 she had a 3 stage procedure for diverticulitis of the sigmoid.

In 1957 the patient had rectal bleeding and study revealed only diverticulosis throughout the colon (Fig. 3).

The patient was admitted with a similar episode in 1959 and required 4000 ml of blood. Again investigation revealed only diverticulosis. Another admission for bleeding occurred in 1960. Elective operation was scheduled, but during induction, the patient had an episode of anoxia with electrocardiographic changes and the operation was cancelled.

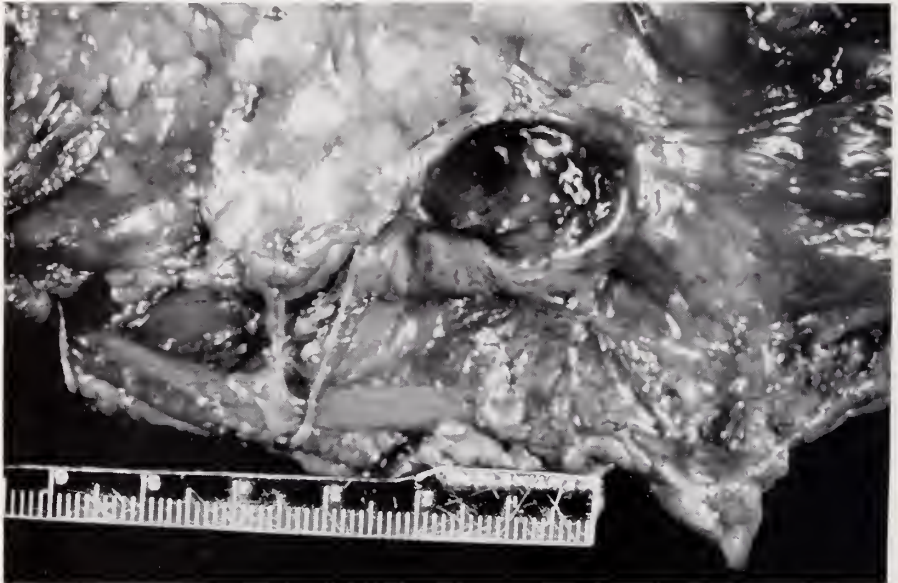


FIG. 2b. Specimen in Case No. 2 revealing the huge diverticulum at hepatic flexure.

Bleeding recurred in March 1962. Again study revealed only diverticulosis. The patient refused operation.

She began passing bloody stools and clots July 31, 1962 and was admitted to the hospital. X-rays again revealed only diverticulosis. A subtotal colectomy with cecoproctostomy was performed electively.

Pathology report: Diverticulosis of the colon. No evidence of diverticulitis.

The patient developed a fecal fistula which prolonged her hospitalization but when last seen in follow up clinic in January 1965 she was well and had no complaints. There was no diarrhea and no recurrence of bleeding.

#### CASE NO. 5

A 61 year old Negro man was admitted March 21, 1963 with 12 hour history of rectal bleeding. There was no other history of gastrointestinal complaints.

Blood pressure was 130/90. Examination was negative except for blood and clots in the rectum. The hematocrit was 39.

Sigmoidoscopy shortly after admission was normal to 25 cm except for blood and clots. Levine tube aspiration revealed a small amount of yellow fluid. Hematologic investigation was within normal limits. During the 48 hours after admission, the patient passed 5 bloody stools with clots and was given 2 units of blood on March 23, 1963. There was no further bleeding and barium enema



FIG. 3. Preoperative barium enema examination of Case No. 4.

revealed multiple diverticula involving the rectosigmoid and descending colon (Fig. 4).

A left hemicolectomy was performed April 5, 1963.

Pathology report: Segment of colon showing diverticulosis. One diverticulum showed a small focus of chronic non-specific inflammation.

When last seen in follow up clinic in October 1963 he had no complaints and there had been no recurrence of bleeding.

#### CASE NO. 6

The patient was a 65 year old male admitted August 26, 1965 with lower abdominal pain and red bloody stools for one day. In 1962 he bled from a

duodenal ulcer and was placed on a diet. Since then he had no gastrointestinal complaints.

On examination his blood pressure was 190/100 and hematocrit was 32. There were no abdominal masses. Rectal examination revealed bloody stool. Gastric aspiration produced a clear fluid which was guaiac negative. Anoscopy revealed brown stool and hemorrhoids.

On August 28, 1965 he began to bleed profusely, had a drop in blood pressure



FIG. 4. Preoperative barium enema examination of Case No. 5.

and complained of pain in the right lower abdomen. His condition worsened rapidly and he was taken to the operating room and an emergency ileocolic resection was performed.

He was reexplored one week later because of peritonitis and a leak at the anastomosis was found and drained. However, his condition gradually deteriorated and he died September 15, 1965.

Pathologic examination demonstrated diverticulosis of the colon with a large diverticulum of the ascending colon showing extensive inflammation and necrosis of vessel walls with hemorrhage (Fig. 5).

## DISCUSSION

Despite the cited reports, diverticular disease of the colon has only reluctantly been accepted as a cause of hemorrhage because of the frequent difficulty in demonstrating the site of bleeding, even on meticulous gross and histological examination of the removed specimen. A recently described method of fixation of the specimen with formalin so that the shapes of the diverticula are maintained seems to be helpful in examining specimens for bleeding sources (14). When a bleeding site can be demonstrated pathologically, the hemorrhage can be traced to a solitary diverticulum which is

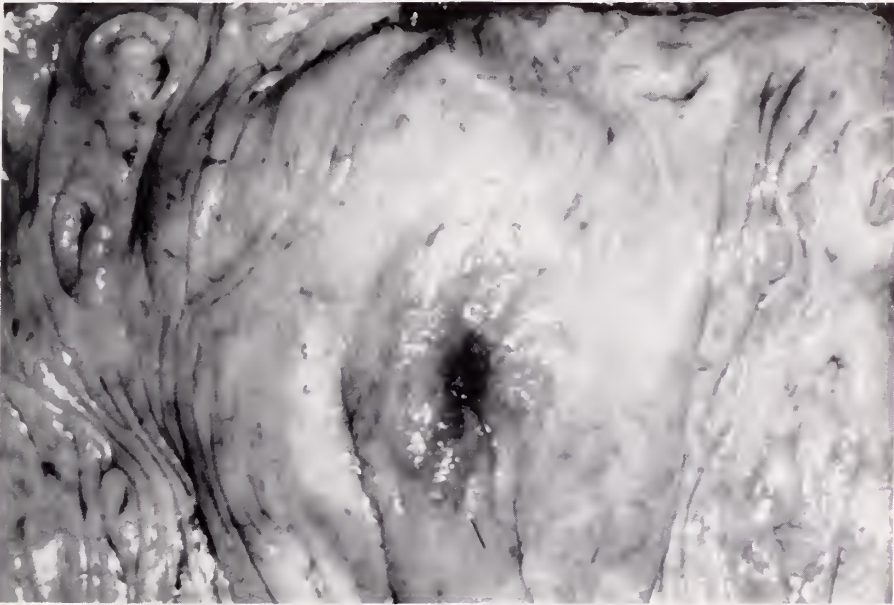


FIG. 5. Specimen in Case No. 6 showing diverticulosis and inflammation of a large diverticulum.

lined with granulation tissue. Occasionally, a small ulceration is present in the colonic mucosa at the mouth of the diverticulum (5). Injection studies (2) have shown a striking concentration of blood vessels in the region of colonic diverticula.

The patients are usually elderly and often have arteriosclerosis and hypertension. They give an almost identical history of a sudden urge to defecate followed by the passage of a large bloody stool, or several such stools. Frequently, there are no other gastrointestinal complaints.

Hemorrhage ceases spontaneously in most patients permitting diagnostic study to be carried out. Goligher (6) and Fraenkel (7) have never had to operate as an emergency. However, Quinn (5) reported 10 of 103 cases in which the bleeding did not stop: 2 died and 8 required emergency surgery. Many of



these patients will have recurrent hemorrhage. Quinn (5) reported a 37 per cent recurrence rate in patients followed one year or more, and Greene (8) noted recurrence of hemorrhage necessitating readmission in 25 of 62 patients.

Those patients who do stop bleeding and who are thoroughly investigated, may reveal no abnormality except for diverticula of the colon, most pronounced in the left colon but often involving all the colon. Only one in four cases shows evidence of diverticulitis. Complete investigation includes proctosigmoidoscopic examination, barium studies of the stomach and small intestine, and colon and hematologic studies.

If massive hemorrhage recurs and again stops, immediate elective resection is indicated. The resection should be extensive enough to remove all or most of the diseased portion of colon. An area of diverticulitis on x-ray in a patient with extensive diverticular disease may not be the source of bleeding, and when possible, the area most extensively involved should also be removed.

If massive bleeding persists, emergency proctoscopic examination and barium enema should be performed promptly depending on the rapidity of the blood loss. If only diverticular disease is found, operation is indicated urgently.

The decision as to what to do at emergency operation is a difficult one, and depends to a great extent on the findings at operation, as well as on barium studies. A thorough search for a carcinoma, polyp or any inflammatory process must be made. If the diverticular disease is limited to one area, that area must be resected. Often, however, the entire colon is involved and subtotal colectomy with ileosigmoidostomy may be necessary. Multiple colotomies and endoscopic examination may reveal the bleeding area (10). One useful method (5) is to occlude the colon into 4 or 5 segments with rubber shod clamps, perform colotomies and aspirate each segment, and watch for refilling. If a segment refills, it should be resected. On occasion, in a very bad risk, it may be possible to identify the bleeding diverticulum, ligate it, and exteriorize the loop of colon involved. Both ileostomy and proximal transverse colostomy have been used with cessation of bleeding in desperately ill patients (11, 12, 13). The involved segment must be resected at a later date.

#### CONCLUSIONS

Based on our recent experience and review of the literature, we feel that massive bleeding from diverticular disease is a definite clinical entity which, apparently, is increasing in frequency or being diagnosed more often. Most patients will stop bleeding spontaneously. Those who do not stop, or who stop for several hours and then again bleed massively, should be operated upon promptly. If bleeding continues, proctosigmoidoscopy and barium enema should be performed. Hematologic examination must also be performed to exclude blood dyscrasias. When diverticular disease only is found, immediate surgery is indicated. If bleeding stops but recurs at a later admission, and again stops, elective resection should be performed.



## REFERENCES

1. Glenn, Frank: Massive Gastro-intestinal Haemorrhage. *Lancet*, 1954, I, 1124.
2. Noer, R. J.: Hemorrhage as a Complication of Diverticulitis. *Ann. Surg.*, 141: 674, 1955.
3. Rives, J. D., and Emmett, R. D.: Melana, A Survey of 206 Cases. *Am. Surgeon*, 20: 468, 1954.
4. Kunath, C. A.: Massive Bleeding from Diverticulosis of the Colon. *Am. J. Surg.*, 94: 914, 1956.
5. Quinn, W. C.: Gross Hemorrhage from Presumed Diverticular Disease Of The Colon. *Am. Surgeon*, 153: 851, 1961.
6. Goligher, J. C.: *Surgery of the Anus, Rectum and Colon*. Springfield, Illinois: Charles C. Thomas, 1964.
7. Fraenkel, G. J., Rectal Bleeding and Diverticulitis. *Brit. J. Surg.*, 41: 643, 1954.
8. Greene, W. W., Diverticulitis of the Colon. *Am. J. Surg.*, 94: 282, 1957.
9. Ulin, A. W., Sokolic, I. H., and Thompson, C.: Massive Hemorrhage from Diverticulitis of the Colon. *Ann. Int. Med.*, 50: 1395, 1959.
10. Jensen, G. L.: Massive Hemorrhage from Diverticulosis of the Colon. *Am. J. Surg.*, 95: 813, 1958.
11. Knight, D. C.: Massive Hemorrhage from Diverticular Disease of the Colon. *Surgery*, 42: 853, 1957.
12. Foster, R. L., Fisher, R. F.: Colostomy as Emergency Treatment for Massive Melena Secondary to Diverticulitis. Case Report. *Am. Surgeon*, 20: 734, 1954.
13. Dunning, M. W. F.: The Clinical Features of Hemorrhage from Diverticula of the Colon. *Gut*, 4: 273, 1963.
14. Rosenberg, I. K., and Rosenberg, B. F.: Massive Hemorrhage from Diverticula of the Colon with Demonstration of the Source of Bleeding. *Ann. Surg.*, 159: 570, 1964.

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# Primary Acquired Red Cell Aplasia in the Adult

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## INTRODUCTION

Since the original description of pure red cell anemia by Kaznelson (1) in 1922 the increasing number of case reports appearing in the literature has made it apparent that further subdivision of this condition is in order. As recently as 1957 (2) it was considered rare enough to be a curiosity. Prior to 1957 Seaman and Kohler (3) had reviewed the literature and reported on ten cases in addition to setting down the following criteria for the diagnosis of pure red cell anemia:

1. Profound chronic normocytic normochromic or macrocytic normochromic anemia with decreased or absent reticulocytes.
2. Cellular marrow exhibiting normally active leucocytic and thrombocytic series but marked hypoplasia to virtual absence of nucleated cells in the red blood cell series.
3. Normal differential and total white blood count.
4. Normal thrombocyte levels and absence of hemorrhagic phenomena.
5. No evidence of extramedullary hematopoiesis.

Cases fulfilling the above criteria have been given various descriptive names, summarized by Tsia and Levin (4). These include: Chronic Hypoplastic Anemia of Blackfan and Diamond, Chronic Congenital Aregenerative Anemia, Congenital Hypoplastic Anemia, Erythrogenesis Imperfecta, Pure Red Cell Anemia, Erythrophthisis, Progressive Post-Infectious Erythrophthisis, Isolated Aplastic Anemia, Anerythropoietic Anemia, Chronic Erythrocytic Hypoplasia, Acquired Erythrocytic Aplasia, Erythroblastophthisis, Essential Erythroblastopenia, Red Cell Aplasia Anemia, Pure (Primary) Red Cell Anemia and Acquired Pure Red Cell Agenesis.

Varied etiologic factors have been associated with or causally related to the onset of pure red cell anemia. Since the hematologic abnormalities as defined by Seaman and Kohler have different etiologies with inherent diagnostic, therapeutic and prognostic implications, it is felt that the following etiologic classification is more useful:

- I. Congenital form of Blackfan and Diamond (5)
- II. Acquired
  - A. Post-infectious of infancy and childhood (6)
  - B. Post-infectious of adulthood (7)

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- C. Toxic (post-toxic exposure) (8, 9, 10)
- D. Neoplastic-preleukemic (11)
  - leukemia (12)
  - associated carcinoma (4, 13)
- E. Associated with thymoma (11, 14-25)
- F. Nutritional (26)
- G. Associated with congenital hemolytic anemia (27)
- H. Uremia (28)
- J. Primary

In reviewing the literature it becomes apparent that many cases of "primary red cell aplasia" have in fact been associated with exposure to various toxins, neoplasms, infections or malnutrition. It is the purpose of this paper to stress the importance of excluding such etiological agents and to describe an unusual case of this entity terminating in aplastic crisis. This has heretofore been unreported.

#### CASE REPORT

A seventy-two year old white male entered The Mount Sinai Hospital January 31, 1963 for shortness of breath and fatigue of three months duration. He had been seen by his private physician two weeks prior to admission when a hemoglobin of 8 Gm per cent was noted. When it was observed that no response to oral iron occurred he was admitted to the ward service of The Mount Sinai Hospital.

Previously he had been admitted to The Mount Sinai Hospital in 1957 for diarrhea of several weeks duration. Barium enema revealed changes consistent with ulcerative colitis. Steroids were given and subsequently tapered and discontinued upon discharge when the patient manifested a dramatic recovery. In the interim there had been no episodes of diarrhea or rectal bleeding and the patient had remained in good nutrition.

In the past history there was one episode of jaundice in childhood. The patient had worked as a curtain maker and was now retired. There was no history of exposure to toxic solvents such as benzol or any history of drug ingestion since the administration of steroids five and a half years prior to admission.

On physical examination he was a well-developed, well-nourished, elderly white male in no distress: Blood pressure 128/64, pulse 90, respiration 20, temperature 98.6°F. Cataracts were present in both eyes. The mucous membranes were pallid. There was no cervical, axillary, or inguinal lymphadenopathy. There were decreased breath sounds and dullness to percussion at the base of the left lung. The heart was unremarkable. Examination of the abdomen did not disclose any palpable organs or masses. Rectal examination was normal as was the neurological examination. No petechial hemorrhages were noted on the skin.

Urinalysis was normal. Biochemical studies of renal and hepatic function

were all within normal limits. Hemoglobin 8.1 Gm per cent, hematocrit 25 per cent, red cells 2.6 million per cu mm, reticulocytes less than 0.5 per cent, M.C.V. 95 cu. microns, M.C.H. 31 gamma gamma, M.C.H.C. 32.5 per cent, platelets 204,000 per cu mm. The white blood cell count was 6,900 per cu mm with 74 per cent segmented forms, 9 per cent eosinophils, 16 per cent lymphocytes and 1 per cent monocytes. Bone marrow aspiration revealed adequate cellularity and an M:E ratio of 7.5:1. The differential was as follows: Myeloblasts 1 per cent, promyelocytes 2 per cent, neutrophilic myelocytes 11 per cent, eosinophilic myelocytes 1 per cent, metamyelocytes 14 per cent, band forms 21 per cent, segmented forms 31 per cent, eosinophils 3 per cent, lymphocytes 1 per cent, plasmacytes 1 per cent, reticulum cells 3 per cent, erythroblasts 1 per cent, normoblasts 10 per cent. Many of the normoblasts were still basophilic. The megakaryocytes were normal in number and maturation.

The Coombs test, gamma and non-gamma, was negative. A bleeding profile was normal. Folic acid was 6.3 micrograms per milliliter, serum vitamin B12 was 404 micromicrograms per milliliter. Serum iron was 247 gamma per cent with total iron binding capacity 263 gamma per cent. Diagnex blue test showed the presence of free hydrochloric acid. Hemoglobin electrophoresis revealed the presence of A hemoglobin only. Serology was negative. Barium studies of the gastrointestinal tract were normal. The chest film showed a small left pleural effusion.

The pleural effusion was tapped and proved to be a clear transudate with negative cell block and culture. A liver biopsy was normal except for an increase in iron pigment. The patient was transfused with a total of four units of whole blood during his hospital stay. He remained afebrile throughout and was asymptomatic except for some residual weakness. Upon discharge February 26, 1963 his hemoglobin was 9.8 Gm per cent, white cell count was 9,900 per cu mm with normal differential, platelets were 435,000 per cu mm and reticulocytes were less than 0.5 per cent. A repeat bone marrow showed results similar to those on admission.

Following discharge the patient required weekly transfusions at the hematology clinic. His only complaints were referable to the profound anemia which ranged between 5.5 Gm per cent and 7.0 Gm per cent. A short admission to the hospital occurred in March 1963 following an anaphylactic reaction to iron dextran, intra-muscular. In June 1963 he required a unit of transfused blood every two to three days. Bone marrow aspiration in June 1963 now revealed a total of 5 per cent red blood cell precursors and he was readmitted to the ward service July 8, 1963.

Examination of the chest once again revealed a small left pleural effusion. The heart was unremarkable other than for a sinus tachycardia. In the abdomen there could now be felt a liver which was one finger breadth enlarged below the right costal margin; the spleen was not palpable. No masses were palpable in the abdomen. There was no lymphadenopathy.

The hemoglobin was now 3.3 Gms per cent with a hematocrit of 9.5 per cent,

red cells 1.12 million per cu mm, M.C.H. 29, M.C.V. 84, and M.C.H.C. 34. The white blood count was 8,000 per cu mm with 82 per cent segmented forms, 1 per cent bands, 14 per cent lymphocytes, 2 per cent monocytes. Platelets were 481,000 per cu mm and reticulocytes 0.1 per cent. Bilirubin was 1.1 mg per cent with 0.1 mg per cent conjugated bilirubin. Haptoglobin determination was 12 mg per cent (normal 50 to 150 mg per cent). Urine was positive for

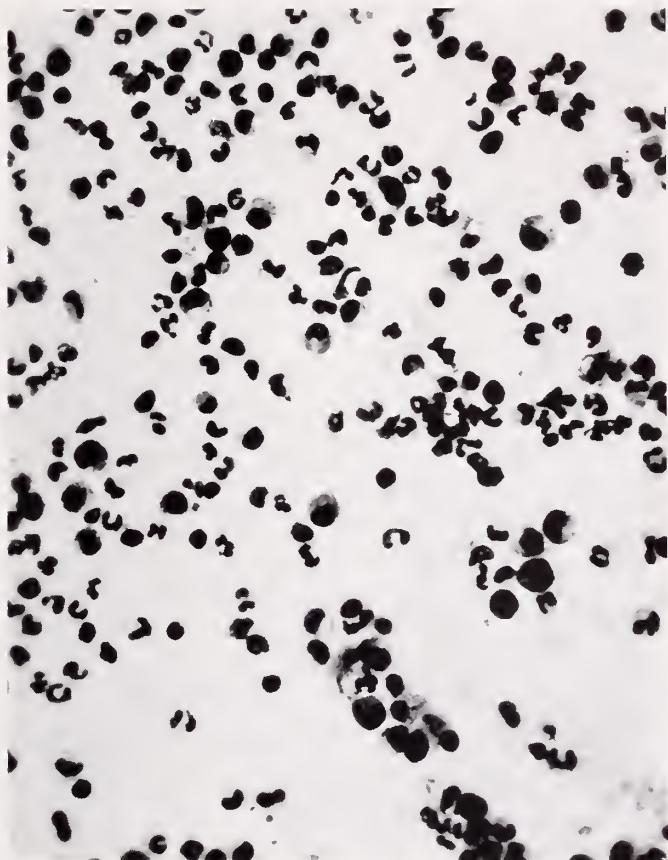


Fig. 1. Sternal marrow aspiration demonstrating active granulopoiesis with virtual absence of red cell precursors (Jenner-Giemsa stain, original magnification  $\times 315$ ).

hemosiderin. Schumm's test was negative. Serum iron was 390 gamma per cent with a total iron binding capacity of 419 gamma per cent. Coombs test was now positive. Tests of renal and hepatic function were normal. The bone marrow aspiration now revealed a virtual aplasia of red cell precursors (Fig. 1). The myeloid series was normal in maturation and number as were the megakaryocytes.

The patient had developed a Coombs positive state and his serum agglutinated the entire panel of sample red cell antigens. He was transfused with packed cells of the most compatible blood of his own type, A+, after priming



with 200 mg of intravenous hydrocortisone. No adverse effects were noted. This was done repeatedly. The antibody was characterized as a warm complement-fixing antibody. The patient was transfused up to 7.0 Gm per cent at which point there was only a minimal tachycardia and no evidence of congestive heart failure. A red cell survival performed shortly after this period revealed a half-life of 11 days using  $\text{Cr}^{51}$ . Blood volume determination revealed a red cell mass of 11.6 milliliters per kilogram of body weight.

The patient was placed on prednisone 40 mg each day by mouth and was given hydrocortisone or methyl prednisolone intravenously prior to each transfusion. On the 25th hospital day the patient was started on stanozolol 18 mg per day. He continued to be transfused every three to four days with one unit of packed red blood cells. On the 68th hospital day, that is after 43 days of stanozolol therapy, he required his last transfusion during this admission. Ten days later his hemoglobin was 11 Gm and reticulocytes were 1.5 per cent. Concomitantly, his white count had fallen to 3800 per cu mm and platelets to 82,000 per cu mm. A bone marrow aspiration performed September 25, 1963 revealed normal erythroid maturation and an M:E ratio of 2:1. The patient was discharged September 27th on 40 mg of prednisone per day and stanozolol 18 mg per day. His white blood cell count was 5250 per cu mm upon discharge.

During the next six months his hemoglobin remained between 11 and 12 Gm. In February 1964 the patient himself decreased his prednisone dosage to 20 mg per day because of some gastric distress. On March 15th he was noted to have a hemoglobin of 7 Gm per cent and the Coombs test was again positive. He was transfused March 27th and readmitted March 28, 1964.

On this last admission the patient was in no distress but appeared chronically ill. His sclera were anicteric. There was no palpable lymphadenopathy. A small left pleural effusion was discernible. The liver was palpated one finger breadth below the right costal margin. Hemoglobin was 8.0 Gm per cent and white blood count was 9,000 per cu mm with a normal differential. His platelet count was 344,000 per cu mm. There was some hypochromia of the red cells on smear and some tear drop cells were noted. Bone marrow aspiration once again revealed complete absence of red cell precursors.

His prednisone was increased to 60 mg per day and 100 mg of testosterone enanthate was given twice a week by injection instead of stanozolol. Pyridoxine was also added to the regimen. After two weeks of hospitalization the patient was noted to be jaundiced with urine positive for bile and he was passing acholic stools. His bilirubin was 7.6 mg per cent with 4.4 mg per cent direct reacting, alkaline phosphatase 20 KA units, thymol turbidity 6.1 units, SGOT 60 units and 105 units, SGPT 218 units. Because of the possibility of a drug-induced hepatitis, the testosterone enanthate was discontinued. A liver biopsy performed May 6th revealed only cholestasis with some bile lakes. The patient's anorexia and lethargy increased concomitantly with a rising bilirubin which on May 11th was 35 mg per cent. At this time his hemoglobin was 7.7 Gm per cent with the white blood count now 2400 per cu mm and the platelets

64,000 per cu mm. Despite the strong possibility of common duct obstruction, his debilitated state, thrombocytopenia, and leucopenia precluded common duct surgery. During the third week of May 1964 he went into frank hepatic coma with a blood ammonia level of  $1.9 \mu\text{g}$  per cu mm. At this time his white blood count fell to 1350 per cu mm and his platelets to 12,000 per cu mm. Despite transfusions, Neomycin enemas, and intravenous steroids, he expired



FIG. 2. Autopsy section of liver demonstrating some liver cell destruction and extensive filling of the canaliculi with bile plugs (H & E  $\times 200$ ).

May 23rd; 19 months after the onset of his present illness, 8 months after his hematologic remission and 2 months following hematologic relapse.

On post-mortem examination the terminal cause of death was found to be bilateral pneumonia. The recurrent pleural effusion was now represented by an area of left pleural thickening. No tumor of the anterior mediastinum was observed. The heart was unremarkable as were the kidneys.

There was no lymph node pathology. The liver was moderately enlarged and revealed massive iron staining of the reticulo-endothelial system. In the portal areas there was some minimal hepatic cell degeneration but no in-

inflammatory cell exudate could be observed. The canaliculi were engorged with bile plugs (Fig. 2). Several stones were observed in the gall bladder but none were found in the common bile duct. The spleen did not reveal extramedullary hematopoiesis or leukemic transformation. The bone marrow was for the most part replaced by fat cells; an occasional island of hematopoiesis was observed.

#### DISCUSSION

This represents the 23rd case in the literature to fulfill the criteria of primary acquired red cell aplasia in the adult. The accompanying table contains a review of all the cases to date. Several heretofore included cases have been omitted from the list because of either the strong relationship to an inciting agent (3, 8, 9, 10, 29), underlying malignancy (4, 11, 13), underlying disease (28), or insufficient data (31). Six of the 16 cases reported by the Mayo Clinic (32) are included in this series since in these cases no history of exposure was recorded, other disease entities were absent, and the follow-up and survival period was sufficiently long to exclude the anemia as the presenting sign of an occult neoplasm.

In reviewing the reported cases several features stand out. With the exception of five cases, the age range was from 46 to 76 years with a median age of 59 years. The male to female ratio was 18:5. More important, however, is the long survival after detection of the anemia, particularly in the era of effective transfusion therapy and also the high percentage of remission or complete recovery noted either spontaneously or with various therapeutic modalities.

Hemolysis has occurred in four instances of acquired idiopathic red cell aplasia of the adult; one case of Loeb and Moore (34), the cases of Eisemann and Damashek (35), Meyer and Bertcher (36) and the present case. With the exception of the first mentioned, all were Coombs positive anemias. The appearance of a Coombs positive state may itself result from transfusion therapy (37) and need not necessarily be causally related to red cell aplasia. In the present case the aplasia antedated the Coombs positive state by at least several weeks. However, in the other instances in which the Coombs test was positive the presence of a coating antibody could no longer be demonstrated when the bone marrow revealed erythropoietic recovery. The implication becomes apparent for a number of cases that an autoantibody is present which simultaneously is attached to the mature red cell and in some way is interfering with the appearance of the proerythroblast in the marrow. Anderson and Ladefoged (24) have suggested that this antibody is directed against erythropoietin-coated red cell precursors.

Terminally our case manifested profound leucopenia and thrombocytopenia and agonally no differentiation between red cell aplasia and aplastic anemia could be made. Loss of white cell and platelet production one year after cessation of erythropoiesis is unique in view of the increased susceptibility of white cells and, secondarily, of platelets to damage from agents known and unknown. Whether leucopenia and thrombocytopenia occurring



terminally was related to the primary process or perhaps was secondary to either hepatic insufficiency, therapy, or sepsis is uncertain.

The various modalities of therapy in idiopathic pure red cell aplasia in the adult are virtually the same as those employed in the other varieties of red cell aplasia or, for that matter, aplastic anemia. Thus transfusions, steroids, androgens, riboflavin, cobalt, pyridoxine, vitamin B12, folic acid and bone marrow transfusion have been attempted in various combinations and with varying success. Complicating Coombs positive hemolytic anemia has been approached with the use of steroids and splenectomy.

Foy and Kondi (10) reported a case which responded to riboflavin. Their case is not included in the accompanying table because of the exposure of the patient to a variety of drugs including the antimalarial mepacrine, a riboflavin antagonist. Recovery was noted following twelve days of riboflavin therapy.

Seaman and Kohler (3) gave cobalt to two patients with secondary red cell aplasia; their second case, a case of overexposure to dry cleaning agents, responded after 64 days of continued therapy. In another report (38) a response to cobalt followed in a case of primary red cell aplasia that had initially responded to splenectomy and later relapsed. In the recent case of Voyce (33), response to cobalt was demonstrated six weeks after doses of 200 milligrams a day. Dosages of cobalt chloride have generally been in the 200 to 300 milligram range. Voyce postulated that cobalt may have interfered with the binding affinity of the elevated gamma globulin demonstrated in his case. No protein abnormality could be demonstrated in other cases successfully treated with cobalt.

The most efficacious therapy in all varieties of marrow aplasia today is the vigorous, prolonged use of androgens at times in conjunction with steroids. The knowledge of the response of the bone marrow to testosterone in the hypogonadal male (39) and the polycythemia that may ensue in woman receiving androgens for breast carcinoma has been utilized in the treatment of all forms of aplastic anemia. Rosenthal and Erf (40) employed testosterone in the treatment of myelofibrosis and, currently, androgen therapy is accepted treatment in this condition. Shahidi and Diamond (41, 42) noted the increased response to steroids when androgens were added in aplastic anemia and this has been noted by others (43, 44, 45).

When employed alone, steroids were associated with complete recovery in 2 out of 6 cases of idiopathic pure red cell aplasia. Of the successes, one was in a case with associated Coombs negative hemolytic anemia and one with associated Coombs positive hemolytic anemia.

Combined androgen-steroid therapy was employed in two cases, with remission in our case after 43 days of combined therapy. However, in the case presented here a failure of the bone marrow on combined therapy occurred six months after clinical remission.

Androgen therapy in other varieties of aplastic anemia appears to be

TABLE I  
*Documented Cases of Primary Acquired Red Cell Aplasia in the Adult*

YEAR	AUTHOR	AGE	SEX	DURATION	HEMO- CYTOMA- TOSIS	CAUSE OF DEATH	COMMENTS
1922	Kazndson (1)	58	M	3 wks	0	anemia	WBC drop, arsenic R <sub>x</sub>
1933	Kloster (50)	62	M	2 yrs	?	broncho- pneu- monia	
1937	Kark (13)	30	M	11 yrs	+	transfusion reaction	10 wk period stable RBC
1942	Mackey (51)	46	M	3½ yrs	+	anemia	maintained on transfusions transient hemolytic anemia, re- covery after splenectomy and post-op steroids
1943	MacFarlane (52)	22	F	2 mos	0	transfusion reaction	
1947	Begenann (53)	59	M	4 yrs +	?	alive	transient hemolytic anemia
1953	Loeb and Moore (34)	17	M	5 yrs	0	alive	
		17	M	2 yrs	0	alive	recovery after splenectomy
1954	Eisenmann and Dameshek (35)	58	F	2 yrs	sidero- sis, of spleen	alive	transient hemolytic anemia
1954	Sakol (54)	51	M	3 yrs	sidero- sis	alive	maintained on transfusions, 0 an- drogens, 0 steroids, 0 splenec- tomy
1955	Fountain and Dales (38)	49	F	6 mos	0	alive	
1960	Meyer and Bertcher (36)	51	M	4 mos	0	alive	recovery after splenectomy
1960	Nicolau and Popesco (46)	59	M	5 mos	0	alive	recovery on steroids
1960	Schaposnick (55)	69	M	17 mos	0	acute pul- monary edema	recovery after bone marrow trans- fusions from two sons
1961	Linsk and Murray (30)	18	M	27 mos	0	alive	hypogammaglobulinemia recovery on steroids



1963	Schmid (32)	76	M	3½ yrs	+	transfu- sion re- action accidental alive	spontaneous remission
		73	F	3½ yrs			
		67	F	5 yrs			
		55	M	3 yrs	+		
		70	M	1 yr		alive	maintained on androgens (8 to 9 Gm)
		72	M	¾ yr	0	alive	spontaneous recovery
1963	Voyce (38)	47	M	5½ yrs	0	alive	gamma globulin spike with cobalt
							terminal aplastic crisis
1964	DiGiacomo, Furst and Nixon	74	M	19 mos	+	hepatic coma	

beneficial when employed for protracted periods. Thus one can not judiciously evaluate androgen therapy until several months have elapsed. On the other hand, if autoimmune mechanisms are seemingly in play, *e.g.*, an associated Coombs positive hemolytic anemia, then steroid therapy alone may be responsible for complete recovery as occurred in one case (36).

There is one report of complete recovery following bone marrow transfusion with the patient's sons as donors (46).

To date splenectomy has been performed in 5 cases of acquired idiopathic red cell aplasia in the adult. Of these, 2 cases met with complete success, both cases having associated hemolytic anemia. Splenectomy was only partially efficacious in another 3 cases (33, 34, 38), both with and without hemolytic anemia. These patients later relapsed and required either steroids or cobalt for sustained remissions. The figures suggest that splenectomy might be of value as a definitive therapeutic measure in cases associated with hemolytic processes.

Two complete spontaneous remissions have occurred with no therapy other than transfusions (32).

#### DISCUSSION

The chance occurrence of red cell aplasia must perforce occasion a search for a causally related factor in much the same way that aplastic anemia engenders an investigation of possible etiologic agents, *i.e.*, drugs and industrial toxins.

Thymomas with and without associated myasthenia gravis currently rank as the foremost etiological syndrome in red cell aplasia in the adult, with more than fifty cases reported (14-25). The immunological questions that are raised in the association remain to be answered. The occasional response to steroids or splenectomy and the disappearance of Coombs positivity during marrow remission suggest an immune pathogenesis. The prototype of such a mechanism causing selective erythroid aplasia may be seen not only in typical autoimmune hemolytic anemia (36) but also following isoimmunization by incompatible blood groups (37) and associated with diseases which are known to display autoimmune phenomena, *i.e.*, leukemia and lymphoma (12, 49). It is of interest that our patient had a diagnosis of ulcerative colitis, often considered an autoimmune disease, several years prior to his hematological diagnosis. In addition to routine laboratory procedures that should be done in every case of acquired red cell aplasia, it is mandatory that lateral tomograms of the chest be performed in that some cases have completely remitted after removal of the anterior mediastinal tumor.

Baar first described a progressive post-infectious pure red cell aplasia in 1928 (7). Kho, reporting from Indonesia (6), alluded to 186 cases in 1500 anemic children. In all 186 either profound malnutrition or fulminant bacterial infections such as salmonellosis or meningitis coexisted. Foy and Kondi also mentioned the absence of erythroid progenitors in the marrow in marasmus and kwashiorkor (26). These factors would undoubtedly become apparent in the investigation of the patient with red cell aplasia.

Toxins that have been associated with the syndrome are much the same as have been implicated in aplastic anemia and agranulocytosis, *i.e.*, benzol (53), sulfa (8), pyrimidon (9), antimalarials (10), and chloramphenicol (49). Gasser (47) has described primary damage to the erythron secondary to a variety of toxic and allergenic agents with the appearance of giant proerythroblasts in the marrow, the condition lasting usually not more than 7 to 10 days. On occasion metabolic states, most notably uremia (28), will be associated with absence of erythroid precursors in the marrow.

Aside from thymomas, a host of neoplastic conditions may be associated with erythroid aplasia; particularly primary hematologic states such as leukemia (12) and lymphoma (49). Primary acquired red cell aplasia in the adult might well be reported more frequently but for the suspicion of the physician, in part justifiable, that the syndrome represents a prodrome of acute or chronic leukemia or a lymphoma variant.

Pure red cell aplasia in the adult, unrelated to toxins, infection, metabolic states, or neoplastic conditions, has been to date extremely rare. The treatment most successful from a perusal of these few cases appears to be akin to the treatment of complete marrow aplasia, *i.e.*, androgens and steroids employed for a protracted period. Splenectomy has been reserved for associated Coombs positive hemolytic anemias unresponsive to cortisone therapy. Terminal leukopenia and/or thrombocytopenia may ensue; whether in the present case this was related to idiopathic bone marrow depression or an associated condition such as hepatic disease or to drug therapy is unknown.

#### SUMMARY

An attempt has been made to characterize acquired red cell aplasia in the adult. Causally related factors must be excluded not only to satisfy diagnostic criteria but because of their prognostic significance. A case is presented which not only satisfies these criteria but also typifies the chronicity of the syndrome and the inherent potential for remission. Terminal aplastic anemia is reported for the first time. A discussion of therapeutic modalities is included as well as an outline of secondary red cell aplasias.

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#### REFERENCES

1. Kaznelson, P.: Zur Entstehung der Blutplättchen. Verhandl. deutsch. Gesellsch. inn. Med., 34: 557, 1922.
2. Whitby, L. E. H. and Britton, C. J. C.: Disorders of the Blood. New York: Grune & Stratton, 1957, p. 472.
3. Seaman, A. J. and Kohler, R. V.: Acquired Erythrocytic Hypoplasia. Acta Haemat., 9: 153, 1953.
4. Tsia, S. Y. and Levin, W. C.: Chronic Erythrocytic Hypoplasia in Adults. Am. J. Med., 22: 322, 1957.

5. Diamond, L. K. and Blackfan, K. D.: Hypoplastic Anemia. *Amer. J. Dis. Child.*, 56: 464, 1938.
6. Kho, L. K., Odang, O., Thajeb, S. and Markum, A. H.: Erythroblastopenia (Pure Red Cell Aplasia) in Childhood in Djakarta. *Blood*, 19: 168, 1962.
7. Baar, H.: Progressive postinfektiöse Erythrophthise. *Folia haemat.*, 35: 111, 1927.
8. Strauss, A. M.: Erythrocytic Hypoplasia following sulfathiazide. *Am. J. Clin. Path.*, 13: 249, 1943.
9. Moeschlin, S. and Rohr, K.: Aplastische Anämie mit jahrlangem vollständigem Fehlen der Erythroblasten (Erythroblastophthise). *Deutsches Arch. klin. Med.*, 190: 117, 1943.
10. Foy, H. and Kondi, A.: A case of true red cell aplastic anemia successfully treated with riboflavin. *J. Path. & Bact.*, 65: 559, 1953.
11. Havard, C. W. H.: An Investigation of Refractory Anemias. *Quart. J. Med.*, 31: 21, 1962.
12. Soutter, L. and Emerson, C. P.: Elective Thymectomy in the Treatment of Aregenerative Anemia associated with Monoeytic Leukemia. *Am. J. Med.*, 28: 609, 1960.
13. Kark, R. M.: Two Cases of Aplastic Anemia. *Guy's Hospital Reports*, 87: 347, 1937.
14. Matras, A. and Priesel, A.: Über eine Gewachse des Thymus. *Beitr. path. Anat.*, 80: 270, 1928.
15. Davidsohn, I.: Clinicopathologic conference case. *Illinois M. J.*, 40: 427, 1941.
16. Ross, T. F., Finch, S. C., Street, R. B. J. and Strieder, J. W.: The simultaneous occurrence of benign thymoma and refractory anemia. *Blood*, 9: 935, 1954.
17. Chalmers, J. N. M. and Boheimer, K.: Pure Red Cell Anemia in Patients with Thymic Tumors. *Brit. M. J.*, 2: 1514, 1954.
18. Weinbaum, J. G. and Thompson, R. F.: Erythroblastic Hypoplasia associated with Thymic Tumor and Myasthenia Gravis: report of a case. *Am. J. Clin. Path.*, 25: 761, 1955.
19. Bayrd, E. D. and Bernatz, P. E.: Benign Thymoma and Agenesis of Erythrocytes. *J.A.M.A.*, 163: 723, 1957.
20. Jacobs, E. M., Hutter, R. V. P., Pool, J. L. and Ley, A. B.: Benign Thymomas and Selective Erythroid Aplasia. *Cancer*, 12: 47, 1959.
21. Kurrein, F.: Pure Red Cell Anemia coincident with Benign Thymoma. *J. Clin. Path.*, 12: 319, 1959.
22. Havard, C. W. H. and Scott, R. B.: Thymic Tumor and Erythroblastic Aplasia. *Brit. J. Haemat.*, 6: 178, 1962.
23. Freeman, Z.: Pure Red Cell Anemia and Thymoma. *Brit. M. J.*, 1: 1390, 1960.
24. Anderson, S. B., and Ladefoged, J.: Pure Red Cell Anemia and Thymoma. *Acta haemat.*, 20: 319, 1963.
25. Crastopol, P., Ellman, A. and Weissman, J.: Refractory Aregenerative Anemia and Benign Thymoma. *New York J. Med.*, 63: 723, 1963.
26. Foy, H. and Kondi, A.: Pure Red Cell Aplasia in Marasmus and Kwashiorkor treated with Riboflavin. *Brit. M. J.*, 1: 937, 1961.
27. Emery, J. L.: Crisis in Congenital Anemia. *Brit. M. J.*, 1: 737, 1954.
28. Loge, J. P., Lange, R. D. and Moore, C. V.: Characterization of the Anemia associated with Chronic Renal Insufficiency. *Am. J. Med.*, 24: 4, 1958.
29. Senda, N.: Aplastic Anemia of Pure Type: Report of a Case and Review of the Literature. *Saishin-Igaku (Newest Med.)*, 9: 354, 1954.
30. Linsk, J. A. and Murray, C. K.: Erythrocyte Aplasia and Hypogammaglobulinemia: response to steroids in a young adult. *Ann. Int. Med.*, 55: 831, 1961.
31. Morita, H.: Various Types of Aplastic Anemia. *Rep. Hemat. Symposium*, 7: 224, 1954.
32. Schmid, J. R., Klein, J. M., Pease, G. L. and Hargraves, M. M.: Acquired Pure Red Cell Agenesis. *Acta haemat.*, 30: 255, 1963.
33. Voyce, M. A.: A Case of Pure Red Cell Aplasia successfully treated with Cobalt. *Brit. J. Haemat.*, 9: 412, 1963.

34. Loeb, V., Moore, C. V. and Dubach, R.: Physiological Evaluation and Management of Chronic Bone Marrow Failure. *Am. J. Med.*, 15: 499, 1953.
35. Eisemann, G. and Damashek, W.: Splenectomy for Pure Red Cell Hypoplastic (Aregenerative) Anemia Associated with Hemolytic Disease. *New England J. Med.*, 251: 1044, 1954.
36. Meyer, L. M. and Berthier, R. W.: Acquired Hemolytic Anemia and Transient Erythroid Hypoplasia of the Bone Marrow. *Am. J. Med.*, 28: 606, 1960.
37. Wasserman, L. R., Stats, D., Schwartz, L. and Fudenberg, A.: Symptomatic and Hemopathic Hemolytic Anemia. *Am. J. Med.*, 18: 961, 1955.
38. Fountain, J. R. and Dales, M.: Pure Red Cell Aplasia Successfully Treated with Cobalt. *Lancet*, 1: 541, 1955.
39. McCullough, E. P. and Jones, T. R.: Note on effect of certain androgens upon red blood cell count and upon glucose tolerance. *Cleveland Clin. Quart.*, 8: 79, 1941.
40. Rosenthal, M. and Erf, L. A.: Clinical Observations on Osteoporosis and Myelofibrosis. *Arch. Int. Med.*, 71: 793, 1943.
41. Shahidi, N. T. and Diamond, K. L.: Testosterone Induced Remission in Aplastic Anemia. *Am. J. Dis. Child.*, 98: 293, 1959.
42. Shahidi, N. T. and Diamond, K. L.: Testosterone Induced Remission in Aplastic Anemia of both Acquired and Congenital Types. *New England J. Med.*, 264: 953, 1961.
43. Gardner, F. G. and Pringle, J. C., Jr.: Androgens and Erythropoiesis. I. Preliminary Clinical Observations. *Arch. Int. Med.*, 107: 846, 1961.
44. Israels, M. C. and Wilkinson, J. F.: Idiopathic Aplastic Anemia. Incidence and Management. *Lancet*, 1: 63, 1961.
45. Kurtides, E. S. and Alt, H. L.: Remission of Hypoplastic Anemia in an adult following combined Androgen and Corticosteroid Therapy. *Quart. Bull. Northwestern Univ. M. School*, 36: 325, 1962.
46. Nicolau, C. T., Popesco, E., Poppa, C., Apateanu, V., Nicoara, S., Grigoriu, G., Butoianu, E. and Fontino, M.: Erythrophtisie traitee per transfusion de moelle aseuse. *Sang.*, 31: 357, 1960.
47. Gasser, C.: Aplasia of Erythropoiesis: Acute and Chronic Erythroblastopenias or Pure (Red Cell) Aplastic Anemias in Childhood, in *Pediat. Clin. N. Amer.*, Philadelphia, W. B. Saunders Company, May 1957, p. 445.
48. Ozer, F. L., Truax, W. E., and Levin, W. C.: Erythroid Hypoplasia Associated with Chloramphenicol. *Blood*, 16: 997, 1960.
49. Bove, J. R.: Combined Erythroid Hypoplasia and Symptomatic Hemolytic Anemia. *New Eng. J. Med.*, 255: 135, 1956.
50. Kloster, J.: Über atypische Anamien. *Folia haemat.*, 51: 251, 1933.
51. Mackey, R.: An unusual Case of Aplastic Anemia with Organ Changes resembling Hemochromatosis. *M. J. Australia*, 1: 172, 1942.
52. Macfarlane and Currie, J. P.: Idiopathic Aplastic Anemia: A report of 4 cases. *Edinburgh M. J.*, 50: 171, 1943.
53. Begemann, H.: Über eine isoliente aplastische Anämie. *Klin. Wchnschr.*, 24: 852, 1947.
54. Sakol, M. J.: Red Cell Aplasia: Report of a Case and Review of the Literature. *A.M.A. Arch. Int. Med.*, 94: 481, 1954.
55. Schaposnik, F. and Vazquez, S.: Aplasia Eritrocítica. *Semana méd. españ.*, 67: 216, 1960.

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# UNUSUAL PROBLEMS IN SURGERY

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## CASE NO. 1

### **Acute Pancreatitis and its Complications**

One of the difficulties in diagnosing acute pancreatitis is that the symptoms and the findings on physical examination are not specifically characteristic of the disease. It is important that the surgeon is certain that other diseases are not present which might prove fatal should an incorrect diagnosis be made. If there is any doubt about the diagnosis the surgeon should not hesitate to operate. However, surgical intervention for acute pancreatitis has in our experience, as well as from the experiences in the literature, increased the morbidity significantly.

The following case is that of one of our patients operated upon for an acute surgical abdomen who proved to have an acute pancreatitis. The postoperative course was stormy and prolonged as a result of a series of complications.

A 29 year old male was admitted to Elmhurst Hospital with complaints of severe upper abdominal pains. The pains began shortly after breakfast the day of admission and were located in the epigastrium, accompanied with nausea and vomiting. The pains were constant and became progressively

worse throughout the day. The patient gave a history of alcoholism for the past four years. He smoked 2½ packages of cigarettes per day. He was considered to be in good health until 3 to 6 months prior to admission when he began to experience frequent short episodes of midepigastriaic pains accompanied with vomiting of clear mucoid fluid. There was no history of hematemesis or melena.

Physical examination revealed a thin acutely ill, anxious male. He was markedly diaphoretic with a pulse of 140, blood pressure 125/100, temperature of 100.2°F. Pertinent physical findings were confined to the abdomen which was moderately distended, diffusely tender over the entire abdomen; more markedly tender in the upper abdomen with rigidity. The liver and spleen were not palpable. There were no abdominal masses palpable. The bowel sounds were hypoactive. Emergency laboratory data included a white blood cell count of 13,000/cu mm with a normal differential, a hemoglobin of 13.8, and a serum amylase of 478. An obstructive series revealed no free air in the peritoneal cavity. The patient was suspected of having an acute pancreatitis, however, a perforated viscus (peptic ulcer) was also strongly considered. Because a perforated ulcer could not be ruled out, it was felt that exploration be performed.

Under general anesthesia, the ab-

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domen was opened through an upper midline incision. There was no evidence of a perforated viscus. Exploration revealed an acute hemorrhagic pancreatitis. The pancreas was enlarged, hemorrhagic and boggy. Approximately 300 to 500 cc of blood-tinged serosanguineous fluid was found in the lesser sac. No further exploration was carried out. The hemorrhagic fluid was aspirated. Multiple Penrose drains and a rubber tube were placed in the lesser sac adjacent to the pancreas for drainage. The abdomen was closed with interrupted wire sutures.

The postoperative course was complicated with delirium tremens which were controlled, but the patient had a septic course with temperatures spiking to 104°F. Purulent drainage was cultured from the drain site and grew a mixed bacterial flora. Appropriate antibiotics were administered with little change in the febrile course. The drain site continued to drain purulent drainage. A sinogram and upper gastrointestinal series revealed an abscess cavity located below and posterior to the greater curvature of the stomach.

Five weeks following the initial exploration, the patient was reoperated upon for drainage of an abscess. At exploration a huge abscess cavity was found extending from the left upper quadrant to the right upper quadrant along the posterior aspect of the greater curvature of the stomach. The cavity contained approximately 200 cc of necrotic pancreatic purulent material. There was a moderate amount of diffuse bleeding from the wall of the abscess cavity which necessitated packing the area to control the bleed-

ing. The abscess cavity was packed. Sump tubes were placed for drainage and the abdomen was closed. Postoperatively blood was noted to drain from the drain site. The bleeding gradually became massive. Approximately two weeks postoperatively the patient required 10 units of whole blood over a short period of time and he was returned to the operating room. Exploration revealed diffuse oozing from the abdominal wall as well as diffuse bleeding from the thick walled abscess cavity. Two moderate sized, actively bleeding vessels in the wall of the cavity were ligated. The abscess cavity was again packed and a Sump tube was used for drainage. Postoperatively there was no further bleeding. The patient's postoperative course was again stormy for the subsequent 4 weeks with spiking temperatures to 103° to 104°F. However, following a spontaneous gush of 100 cc of pus from the drain site he immediately began to show signs of improvement and his temperature rapidly returned to normal. He began to tolerate his feedings well. The abscess cavity became progressively smaller and after 79 hospital days the patient was discharged.

Two days following discharge from the hospital the patient reappeared in the Emergency Room with chills, fever, and abdominal pains. He appeared acutely ill with a temperature of 104.2°F, a pulse of 100. His abdomen was mildly distended and diffusely tender. There was a slight drainage from the old drain site. Laboratory data included a white blood cell count of 12,000/cu mm with a shift to the left and serum amylase of 59 units. The patient was placed on

antibiotics with the suspicion of another abscess. On the fourth hospital day of this admission, small intestinal contents drained from the drain site. An upper gastrointestinal series and fistulogram revealed an enterocutaneous fistula from the proximal jejunum. During the subsequent two weeks the fistula drained approximately 2000 to 3000 cc of fluid per day.

The patient was maintained on intravenous fluids and nothing by mouth. Electrolytes were maintained within normal levels. He ran a febrile course and the enterocutaneous fistula continued to drain without evidence of healing. A recurrent abscess was suspected which in its proximity had involved small bowel and caused a small bowel fistula. Since the presence of the abscess was most probably responsible for preventing the fistula from healing a re-exploration and drainage of the abscess was considered necessary. Therefore, after 14 days the patient with a progressive downhill course and without evidence of the fistula healing was again explored. The abdomen was entered through an inverted V skin incision in the epigastrium away from the previous scars and draining fistula. The abdomen contained extensive adhesions. The abdominal organs were edematous, friable, and were firmly adherent to each other. The abscess cavity was located posterior to the transverse colon and greater curvature of the stomach near the head of the pancreas. A segment of proximal jejunum was incorporated into the anterior wall of the abscess cavity, and from this involved segment a wide open fistula approximately 4 to

5 inches from the ligament of Treitz was identified. Adjacent to this large fistula were present 3 or 4 tiny fistulas. The segment of bowel could not be mobilized nor was it possible to identify and isolate any loop of small bowel, because of the intense inflammatory process matting all structures together. Since the segment of bowel and its fistula were situated adjacent to the stomach, it was feasible to anastomose the stomach to the fistula. The fistulas were connected so as to form one opening. The edges were debrided and a gastrojejunostomy was performed. Two gastrostomy tubes were separately placed. One tube was directed through the anastomosis into the proximal limb of the jejunum for decompression and the other tube was directed through the anastomosis into the distal jejunum for feeding purposes. Penrose drains and rubber catheters were placed in the abscess cavity and the abdomen was closed. On the fifth postoperative day an anastomotic leak became evident. The course was further complicated by an infected wound which completely dehisced. However, with local care to the wound, the administration of intravenous fluids and antibiotics the patient very slowly improved. He became afebrile. The amount of fistula drainage gradually diminished. A trial of oral feedings was started which the patient tolerated well and the fistula closed completely by the twenty-fifth postoperative day. He then made great strides toward recovering with a progressive increase in appetite, weight gain, and general feeling of well being. At the end of his illness the patient weighed 80 pounds.

An upper gastrointestinal series re-

vealed prompt passage of contrast material from the stomach through the gastroenterostomy as well as through the duodenum without evidence of leakage. At the time of discharge from the hospital the patient weighed 105 pounds.

During examination in the Surgical Clinic 2 months following discharge from the hospital the patient looked well and stated that he felt very well. His appetite was excellent, he had no gastrointestinal complaints or abdominal pains. His weight was 150 pounds.

**DISCUSSION.** This case illustrates the major complications that may develop as a sequela to acute pancreatitis. As inflammation, necrosis, and secondary infection develop, pancreatic abscess follows.

Delayed hemorrhage which occurs about 10 days or more following the onset of acute pancreatitis seems to have as a basic feature secondary infection of the necrotic pancreas. Hemorrhage may be massive from the gastrointestinal tract often due to involvement of adjacent structures by the infected necrotic pancreatic tissue and abscess. Bleeding may also occur from the bed of the infected pancreatic tissue as was the case with our patient.

Perforation of a pancreatic abscess has been reported to occur into the stomach, duodenum, small and large bowel. Our patient demonstrated a perforation of the proximal small bowel adjacent to the abscess. We felt that our approach to the intestinal fistula was of interest particularly in the presence of the adjacent abscess and general abdominal inflammation. One can only speculate as to whether the patient would have developed the

various complications had he not been operated upon initially. However, once complications occur, multiple operations may be necessary and frequently life-saving.

## CASE NO. 2

### **Massive Ascites Secondary to Pancreatitis**

The source of ascites, especially in the alcoholic, is usually the liver. In the differential diagnosis of massive ascites, pancreatitis is rarely considered in spite of the fact that this gland, especially in an acutely inflammatory state, is the site of production of variable amounts of characteristic peritoneal fluid. This fluid is usually serous or serosanguinous and is characterized by high concentrations of pancreatic enzymes.

A few scattered reports describe ascites of pancreatic origin (1, 2). Speculation concerning the cause of ascites in this condition includes obstruction and/or thrombosis of the portal vein or its tributaries, internal pancreatic fistulae (3), encroachment of pancreatic cysts or pseudocysts on adjoining structures, and chemical, irritative peritonitis. Recurrent massive chylous ascites has also been reported as a consequence of chronic relapsing pancreatitis (2).

The case described below is one in which exploratory laparotomy with internal and external drainage of pancreatic pseudocysts resulted in a subsidence of massive ascites which caused severe symptoms of malignant cachexia in a young alcoholic man.

A 27 year old man was admitted to Mount Sinai Hospital with a chief

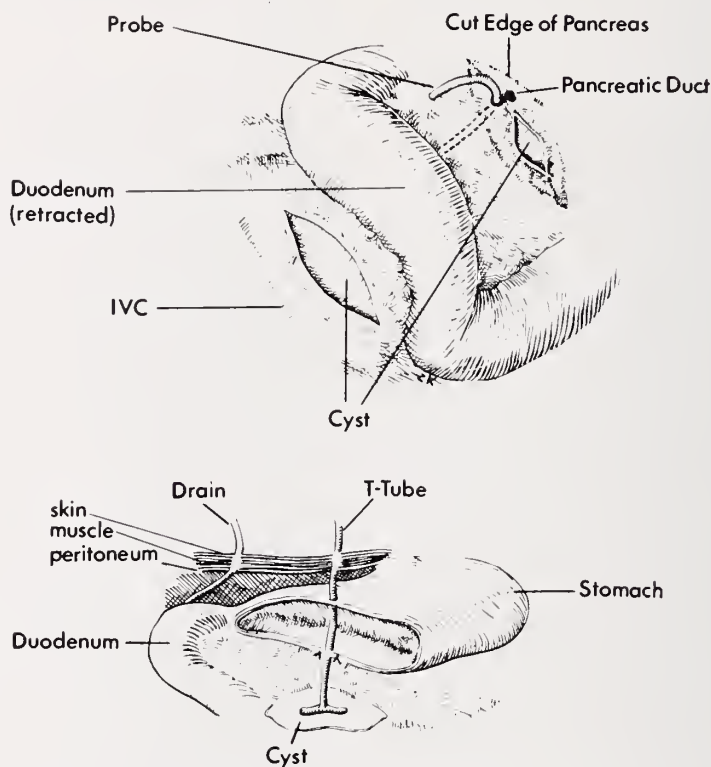


complaint of upper abdominal pain, abdominal swelling, and a twenty pound weight loss over the month prior to admission. The patient gave a history of alcoholism in the past nine years, and admitted to the ingestion of two to three bottles of cheap wine daily. During the year prior to ad-

suggestions, the patient did not stop drinking and did not follow the recommended diet.

Recently, he noted occasional ankle swelling, left chest pain, and bouts of shortness of breath related to the degree of abdominal distension.

The patient had been employed as



Case No. 2, Fig. 1. Operation findings and treatment.

mission there had been multiple admissions to other hospitals for pancreatitis, upper gastrointestinal bleeding, and ascites. He had been told of "liver trouble" at one hospital, and a diagnosis of acute pancreatitis was made one year before at another institution. There was no past history of hepatitis or jaundice. Despite multiple warnings and dietary regimen

a house painter up to two years before admission but denies excessive exposure to known hepatotoxins.

Physical examination revealed a thin, chronically ill male with a temperature of 99°F., pulse 100, respirations 24, and blood pressure 120/90. He was pale and anicteric. There was a male escutcheon, and he was free of vascular spiders, liver palms, and



breast enlargement. His lungs were clear but his diaphragm did not move well and dullness to percussion was noted at both lung bases. The abdomen was markedly distended and tense; a fluid wave was elicited. The liver and spleen were not palpable or ballotable. The genitalia were normal, the extremities without edema, and the neurological examination was within normal limits. Laboratory data included a hemoglobin of 14.4 gm, a white blood count of 11,000 cu mm, with a shift to the left, sedimentation rate of 20 mm, urine: normal, fasting blood sugar: 78 mg per cent, BUN: 13, sodium 136 mEq/L, chloride 102 mEq/L, potassium 4.4 mEq/L,  $\text{CO}_2$ : 31.5 mEq/L, bilirubin total 0.7 mg per cent, indirect 0.3 mg per cent, total cholesterol 140 mg per cent, calcium 9.0 mEq/L, phosphorus 4.8 mEq/L, alkaline phosphatase 2.3 B.L. units (normal), thymol turbidity 10, SGOT: 9, SGPT: 6, cephalin flocculation 1 plus, total protein 6.1 gm per cent, albumin 2.6 gm per cent, globulin 3.5 gm per cent, serum amylase 307 units, prothrombin time: patient 13 seconds, control 12 seconds, stool guaiac negative, stool for ova and parasites negative, latex fixation negative, BSP 4 per cent retention, PPD strongly positive. Abdominal diagnostic tap revealed a clear yellow fluid with a specific gravity of 1.012, pH alkaline, many red and white blood cells, no tumor cells, total protein 6.2 gm per cent, amylase of 640 units, and culture for AFB was negative. A gastrointestinal series revealed a normal esophagus without varices, a normal stomach, duodenum and duodenal sweep and no pancreatic masses. A barium enema was normal and a chest

x-ray revealed a small left pleural effusion.

The patient continued to accumulate abdominal fluid rich in enzyme content despite repeated paracentesis and treatment with steroids, INH, and intravenous colloid solutions. Despite nasogastric suction and administration of large doses of anticholinergic drugs, his preoperative course was marked by repeated episodes of acute pancreatitis with serum amylase estimations up to 5,000 units. Three hundred cc of left pleural fluid was removed; it too was rich in amylase and closely resembled the fluid obtained by paracentesis.

Because of an inability to control the patient medically, he was transferred to the surgical service for some form of surgical treatment. He was considered an extremely poor anesthetic and surgical risk because of his extreme cachexia. Following a second drainage of 1,300 cc of left chest fluid and over 2,000 cc of abdominal fluid and rehydration with intravenous electrolyte and colloid administration, the patient was considered ready for surgery.

Under nitrous oxide-oxygen anesthesia, the abdomen was opened through a long upper transverse incision. There was extensive fibrinous exudation over the entire peritoneal cavity; by blunt and sharp dissection the pancreas was exposed. Its general appearance was more normal than expected; its consistency was firm; it was not very edematous or grossly inflamed; its surface wept serous fluid after it was wiped dry. An aspirating needle was placed in the body of the gland in a search for a cyst and after a few attempts a cavity was entered

and cloudy grey fluid was obtained. An incision was made in the body of the pancreas following the needle tract and as the incision was carried down to the cyst a normal sized pancreatic duct was first encountered and divided. Probes were passed into the duct both proximally into the duodenum and distally to the tail of the gland without any difficulty, and a number three Bakes Dilator was passed with ease into the duodenum (Fig. 1). No calculi, concretions, sludge or strictures were encountered. Further incision revealed the entire cystic cavity on the most dorsal portion of the pancreatic body with a total capacity of about 50 cc. Further exploration of the pancreas revealed a second cyst in its retroduodenal portion which was also incised. Biopsies of the cyst walls were taken, and specimens of fluid for analysis and culture. The cyst of the body of the pancreas was intubated with the T portion of a T tube, and the pancreatic substance closed about it with multiple sutures. The long arm of the T tube was then brought through both walls of the stomach using pursestring sutures for each penetration of the gastric wall. The posterior gastric wall was then sutured to the pancreatic capsule with interrupted silk sutures when a gastrostomy tube was brought out alongside the T tube. The retroduodenal cyst was drained with a rubber tube brought out the abdominal wall through a stab incision. A Witzel feeding jejunostomy was established prior to abdominal wall closure.

The patient withstood the procedure well. Biopsy reports revealed that both cysts were pseudocysts, and

that the pancreatic and liver specimens were normal.

Postoperatively ascites did not recur. Varying amounts of pancreatic fluid drained through and alongside the T Tube; the drain to the other cyst drained little if at all. Jejunostomy feedings were begun on the third postoperative day with added Vio-kase. The steroid dosage which had been raised for surgery was gradually tapered. The patient began to gain weight. One month following surgery, after an unsuccessful attempt at radiographic studies through the T tube, and some hours after removal of this tube, he developed a fever of 104°F. He was treated with Penicillin and Chloromycetin for an intra-abdominal infection which manifested itself with fever, pain and epigastric tenderness. His fever and leucocytosis returned to normal over the next few days. Gastrointestinal series at this time revealed a widening of the duodenal sweep compatible with a pancreatic mass. Repeat gastrointestinal series a few days later indicated a decrease in the size of the mass. The jejunostomy and gastrostomy tubes were removed, and the patient was discharged to follow-up in the outpatient department two months after surgery.

**DISCUSSION.** This case illustrates that massive abdominal distension secondary to intraperitoneal fluid may be of pancreatic origin. Even in the alcoholic, with ascites, where hepatic dysfunction is etiologically most likely, the pancreas should not be overlooked as a possible cause of the ascites. Thus, diagnostic paracentesis should include an enzyme determination.

The pathogenesis of the persistent

preoperative ascites in this patient is conjectural. There was no evidence of major duct obstruction but, undoubtedly, minor duct and ductular obstruction existed. The pseudocysts found at operation were not very large, and did not appear to be obstructing or compressing a major vessel, nor did they appear to be communicating with the peritoneal cavity via an internal fistula. One can postulate that some source of communication did exist, that fluid wept from the pancreatic surface as was noted at surgery, and that these in addition to the chemical irritative effect of the pancreatic juices on the generalized peritoneum resulted in the continuing fluid collection.

The suggested surgical therapy for massive ascites varies from pancreatectomy due to pancreatitis to cyst drainage via internal or external fistulae to duct drainage (1). Roentgen

therapy has been reported with apparent success in a case of chronic relapsing.

The prognosis for this patient is not good unless his alcoholism can be stopped; undoubtedly repeated attacks of pancreatitis with or without ascites will occur, and, if he survives these, the ravages of pancreatic insufficiency and diabetes will probably ensue.

#### REFERENCES

1. Barva, R., Villa, F., and Steigmann, F.: Massive Ascites Due to Pancreatitis. *Am. J. Digest. Dis.*, 7: 900, 1962.
2. Gambiu, E. E., Walters, W., and Scanlon, P. W.: Chronic Relapsing Pancreatitis with Extensive Subacute Peritonitis and Chronic, Relapsing Massive "Chylous" Ascites. *Am. J. Med.*, 28: 668, 1960.
3. Hardy, J. D. and Bowlm, J. W.: Some Implications of Pancreatic Disease. *Ann. Surg.*, 145: 848, 1957.

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## Splenic Abscess

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Abscess formation in the spleen was described by Hippocrates and has been reported regularly in the medical literature through the subsequent decades. Surveys of autopsy material during the pre-antibiotic era, when suppurative disease was a more frequent cause of death, revealed a 0.4 per cent incidence of splenic abscess (9). These splenic abscesses generally were multiple and associated with suppuration in many other organs. In modern experience, splenic abscess presenting as primary clinical problem is uncommon. This is particularly true in the temperate zones of the world where diseases affecting the spleen primarily are relatively rare. Two cases of splenic abscess encountered on a general hospital surgical unit in New York City were considered of sufficient surgical interest to warrant their presentation and a review of the literature on this subject.

### CASE 1

A 57 year old Caucasian female was admitted to the Greenpoint Division, Mount Sinai Hospital Services, Brooklyn, New York February 3, 1964 with complaints of weakness, mild pain in the left shoulder and night sweats for the previous two weeks. The patient, a known diabetic and hypertensive with a history of previous myocardial infarction, had suddenly collapsed on the day of admission. On admission, the patient was confused and apathetic and complained of severe low left lateral chest pain. She appeared dyspneic and markedly cyanotic, with rapid shallow respiration. Her skin was cool and clammy. The pulse rate was 100, the blood pressure 140/85 and the temperature was 99.6°F.

The patient responded to verbal commands, but initially she kept her head and eyes turned to the left, staring vacantly into space. She answered questions irrelevantly and inaccurately. There were faint crepitant rales at both lung bases and the heart sounds were faint and distant. The abdomen was flat, soft and exhibited no tenderness, and the liver edge was felt three finger breadths below the right costal margin.

The patient had been receiving digitoxin 0.1 mg daily, hydrochlorothiazide 50 mg daily, tolbutamide 500 mg twice daily, pentaerythritol tetranitrate three times daily and hydroxyzine hydrochloride 10 mg twice daily.

Electrocardiogram revealed an old posterior wall myocardial infarction, evidence of left ventricular hypertrophy and digitalis effect. There was mild right upper extremity atrophy related to birth trauma. There was no clinical

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response to intravenous dextrose. The cyanosis improved with oxygen inhalation and verbal stimulation to ventilate.

Within several hours after admission the patient complained of severe abdominal pain and diffuse tenderness and rigidity were noted. Her temperature at this time had risen to 103°F. The hemoglobin was 13.2 gm per cent, with a white cell count of 13,500. The differential count revealed polymorphonuclear leukocytes 77, bands 8, lymphocytes 12, monocytes 2 and metamyelocytes 1. The urinalysis showed 10 to 15 white blood cells per high power field, 4 to 8 red blood cells per high power field, 1 plus albumin, 1 plus sugar and a trace of acetone. The serum amylase was 151 units. Fasting blood sugar was 475 mg per cent the blood urea nitrogen 43 mg per cent, creatinine 1.9 mg per cent. Diagnostic paracentesis was performed and a large amount of brownish non-odorous fluid was obtained. Electrolyte determination revealed a serum sodium of 140 mEq/L, potassium of 4.2 mEq/L and a chloride of 108 mEq/L. The patient weighed 59 kilos and a blood volume determination, using a radio-iodinated serum albumin dilution technique, was normal at 4100 cc.

X-ray examination of the chest was negative. Abdominal films revealed an isolated dilated loop of small intestine in the mid-abdomen.

The patient was treated initially with intravenous insulin, plasma and saline solution. By the evening of the day of admission, it was quite clear that the patient suffered from acute peritonitis. With a presumptive diagnosis of mesenteric artery embolus with infarction of the intestine, the patient was explored.

The abdomen was entered through a left paramedian upper abdominal incision. Approximately 750 cubic centimeters of turbid, tannish, odorless fluid was found and aspirated. Cultures were taken which subsequently showed *Bacillus bacteroides*. Initial exploration failed to reveal any evidence of infarction or perforation of the intestinal tract. The appendix, gallbladder, biliary system, uterus, fallopian tubes and ovaries were normal. On careful inspection of the organs in the left upper quadrant, a number of dense adhesions were noted between the greater curvature of the stomach and lateral parietes and in the region of the colophrenic ligament. Purulent material could be seen coming from between these adhesions with each descent of the diaphragm. Further dissection in this area revealed a moderately enlarged spleen with a dense fibrotic reaction about its capsule, adherent to the diaphragmatic peritoneum. At its lower pole, there was a perforation from which issued purulent material. Since the spleen clearly could not be delivered in the usual fashion, it was elected to ligate the splenic artery and vein primarily. The lesser sac was entered by dividing the short gastric vessels. On securing the splenic artery and vein with ligatures, there was an improvement in the general condition of the patient, with a rise in blood pressure and a slowing of the pulse.

The spleen was then removed piecemeal and was found to contain a large, well-established abscess cavity. Hemostasis was secured and a large tubular drain, together with several penrose drains, were placed in the left subphrenic space and brought out through a lateral stab wound. The abdomen was then



closed with interrupted figure-of-eight stainless steel wires through peritoneum and fascia. The skin was closed with interrupted silk sutures. During the operation the patient received 300 ml of plasma with 50 gm of mannitol in dextrose and saline.

Postoperatively the patient's general condition was markedly improved although she remained somewhat confused. She was treated with large doses of aqueous penicillin and chloromycetin intravenously during the first postoperative week. Her drains were advanced and removed on the eighth postoperative day. Her mental state improved slowly and she was discharged thirty-eight days after admission.

One month later the patient was admitted to Kings County Hospital because of acute congestive heart failure and acidosis. She was treated with anti-coagulants and digitalis because of suspected pulmonary emboli. Her blood urea nitrogen rose gradually and the patient expired on the fourteenth hospital day.

Postmortem examination revealed generalized arteriosclerosis with marked atherosclerosis of the coronary vessels. There was a recent myocardial infarction of the posterior wall and an old antero-septal infarction. Mural thrombi were found at the apex of the left ventricle. The kidneys revealed moderate arteriolar nephrosclerosis and diabetic glomerular sclerosis. The lungs revealed multiple pulmonary emboli bilaterally, with multiple pulmonary infarcts, both recent and old. The cause of death was recent myocardial infarction, complicated by pulmonary thromboemboli and infarction.

Pathologic examination of the removed spleen revealed a marked chronic perisplenitis with fibrosis, indicating long-standing inflammatory disease of that organ. The abscess cavity within the spleen was large, with a thick pyogenic membrane. Culture and pathologic sections revealed gram negative *B. bacteroides* organisms (Figs. 1a, 1b). The abscess cavity was solitary and had perforated spontaneously through the lower pole of the spleen.

## CASE 2

A 24 year old Negro male was admitted to the Medical Service of The Mount Sinai Hospital June 22, 1965 with chief complaint of chills, fever and left upper quadrant abdominal pain of 5 days duration. The patient had had numerous previous admissions to this hospital for treatment of painful sickle cell crises. He was known to have a hemoglobinopathy of the SC type. His left upper quadrant abdominal pain was described as sharp, aggravated by respiratory motion and radiating to the left shoulder. The pain persisted, his urine appeared darker than usual and on the day prior to admission he developed diarrhea with 9 to 10 loose stools. On admission to the hospital his temperature was 104°F., pulse rate 112, blood pressure 110/85 and respirations 20. There were decreased breath sounds at the left lung base posteriorly, with fine inspiratory rales and expiratory wheezes. On examination of the abdomen, the liver was felt 1 to 2 finger breadths below the right costal margin and the spleen was enlarged 3 to 4 finger breadths below the left costal margin and was

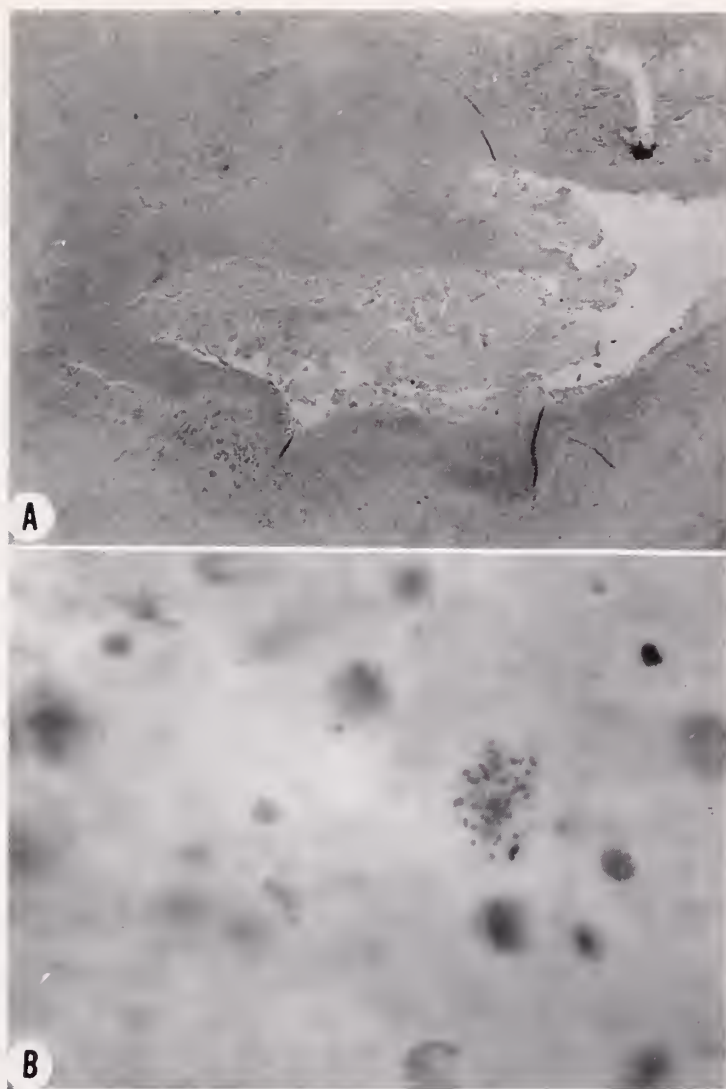


FIG. 1a (Case 1) One of the abscesses of the spleen.  
FIG. 1b (Case 1) Gram negative bacteria in the spleen.

firm and tender. Rebound tenderness could be elicited in the left upper quadrant and there was generalized gaseous distention of the abdomen. The initial white cell blood cell count was 9,500 with a differential of 18 neutrophils, 49 bands, 10 lymphocytes, 22 monocytes and 1 basophile. The hemoglobin was 10 gm per cent, hematocrit 31. The sickle cell preparation showed 10 per cent sickling. Urinalysis revealed 1 plus albuminuria and acetonuria.

During the first week of hospitalization, the patient appeared slightly icteric and had a relatively low reticulocyte count despite a fall in hemoglobin. A blood culture grew *Salmonella enteritidis* which was also present in the stool.

The serum iron was 16  $\mu\text{g}$  per cent with a total iron binding capacity of 178  $\mu\text{g}$  per cent. Blood chemistries revealed an alkaline phosphatase of 27 KAU, an amylase of 630 units and SGOT of 440 units. The patient was treated with penicillin, streptomycin and chloromycetin but continued to run a high temperature of 104 to 105°F. Abdominal pain persisted and the bilirubin rose to 9 mg per cent. Chest X-ray revealed a pneumonitis at the left base with elevation of the left diaphragm. The patient did not respond to antibiotic therapy and, during the second hospital week, oxacillin was introduced; when that failed, neomycin was given parenterally. During the third hospital week, his



FIG. 2 (Case 2) Gastrointestinal series showing displacement of the stomach by the splenic mass and air bubbles within it (arrows).

condition improved somewhat and the pulmonary findings cleared on serial radiographs. During the fourth hospital week, however, the patient's temperature again rose considerably and his sensorium became clouded. He passed several foul smelling, red-brown stools per rectum. A cholecystogram done at this time was normal, but a gastrointestinal series performed at the end of his fifth hospital week revealed an enlarged spleen displacing the stomach medially. A number of gas bubbles were demonstrated within the pulp of the spleen (Fig. 2). The clinical course and radiographic picture being quite characteristic of "tropical" splenic abscess, the patient was transferred to Surgical Service for splenectomy. Prior to surgery he received 2 units of whole blood.

The spleen was approached through a long left paramedian incision. It was found to be moderately large and densely adherent to all the surrounding

structures. Prior to dissection around the spleen, the splenic artery and vein were approached through the lesser omentum and ligated in continuity. The splenic dissection was very difficult and the splenic pulp was entered at several points. There was a moderate amount of bleeding attendant on the dissection and the patient received three units of whole blood during the procedure. The spleen was finally delivered from the abdominal cavity and its pedicle doubly ligated. After removal of the spleen, there was continuous oozing from its diaphragmatic bed despite a prolonged effort to achieve complete hemostasis. Consequently, a gauze packing was placed in the left subphrenic space and brought out with a tubular drain and three Penrose drains through a large left lateral stab wound. The wound was closed with interrupted #28 wire sutures through peritoneum and fascia. Because of the contamination produced by the mobilization of the heavily infected spleen, cutaneous sutures were placed but were not tied initially, to allow for a secondary closure.

The surgical specimen was somewhat enlarged, weighing 565 grams. The capsule was absent in several areas. On cut section the parenchyma was dark red and the follicular pattern obscured. In one area there was a large splenic infarct containing brownish necrotic material. On microscopic section the spleen showed hyperemia, sickling of red cells, hemosiderosis, normoblastic foci and areas of infarction. Cultures of the necrotic splenic pulp grew *Salmonella enteritidis* and *Escherichia coli*.

Postoperatively the patient received penicillin, ampicillin and cephalothin. He remained febrile until the eighth postoperative day when, under general anesthesia, the packing and drains were removed and a double sump tube inserted into the operative area. The patient was then treated with continuous irrigation and aspiration of the splenic bed with sterile saline solution. Gradually the temperature returned to normal and the drains were progressively shortened and removed entirely on the twenty-fifth postoperative day. Feeling well, he was discharged from the hospital one month after surgery. Shortly after discharge he returned to the Outpatient Clinic where a small purulent collection in the drain tract was evacuated. From that time he has done well with the exception of some neurosensory hearing loss, presumed to be secondary to streptomycin and neomycin toxicity.

#### DISCUSSION

The first patient is only the fifth reported case of intraperitoneal rupture of a splenic abscess diagnosed premortem and only the second reported survivor (7). Unless a diagnosis of splenic abscess has been previously made, the acute event of rupture appearing as a perforation of an intra-abdominal viscus is almost always misdiagnosed. Proper conduct of the operative procedure, upon making the diagnosis at laparotomy, merits some discussion in view of the difficulty encountered in removing an adherent infected spleen. Remarkable improvement in the general condition of the patient on ligation of the splenic pedicle and aspiration of the peritoneal fluid, as previously observed by Whelan, was confirmed by our experience. Primary control of the splenic pedicle



allows a safe splenectomy to be carried out by reducing the potential blood loss. By carefully packing off the operative area in the left upper quadrant, even piecemeal removal of the spleen can be accomplished successfully without undue contamination of the remainder of the peritoneal cavity. Adequate sump suction drainage of the left subphrenic space must be established because of the likelihood of contamination and subsequent infection of this area. Prompt culture and antibiotic sensitivity tests of the organisms in the spleen are mandatory for judicious selection of appropriate antibiotics.

The tan, turbid, odorless fluid found in this patient resembles the description of fluid found in other similar cases previously reported (1, 4) and is apparently characteristic of this condition.

In reconstructing the pathogenesis of this case, one notes the premonitory cerebral signs and the finding of an intraventricular mural thrombosis suggesting an embolic shower resulting in splenic infarction as well as transitory cerebral ischemia. No other abscesses were found intraperitoneally and no other primary source of infection could be found which mitigates against generalized septicemia. One must conclude then that secondary infection of a splenic infarct was the underlying etiology in this case.

The etiology and pathogenesis of splenic abscess is multifold. With the exception of the gonococcus, every known pathogenic bacterial organism has been found and reported in the spleen. In the temperate zones of the world, splenic abscess is most often caused by bacteremia, with septic emboli localizing in the spleen. Bland splenic infarction may also occur and secondary infection supervenes. It is estimated that 75 per cent of all reported cases of splenic abscess have this etiology (3). Billings (6) reporting on 3,600 autopsies, found 24 splenic abscesses in 141 splenic infarctions. Although generally the site of entry is arterial, pyelophlebitis of the portal venous system can result in splenic suppuration.

In the majority of cases, there is a known primary focus of infection. Some of those reported include endocarditis, pneumonia, lung abscess, empyema, dental infections, otitis, mastoiditis, peritonsillar abscess, pelvic suppurative disease, endometritis (septic abortion), thrombophlebitis, appendicitis and skin and soft tissue infections, especially in the presence of diabetes.

The primarily diseased spleen is also susceptible to suppurative complications. In the older literature and in cases reported from tropical areas, malaria, typhoid fever and relapsing fever are common underlying conditions. Hydatid and dermoid cysts, as well as amoebomas occurring in the spleen, have become secondarily infected. Primary blood dyscrasias, including leukemia and sickle cell disease, predispose to splenic abscess. In a series of six tropical acute splenic abscesses reported from Nigeria, five patients had sickle cell disease (5). In these cases, the abscess may be a sterile postinfarction phenomenon. In the second patient presented in this paper, the abscess resulted from such a splenic infarction secondary to sickle cell SC hemoglobin disease. The offending organism here was *B. bacteroides*.

A small percentage of cases are secondary to post-traumatic subcapsular



hematomas. Inlow (2) in 1927 reported 24 such cases treated surgically with a 38 per cent mortality. A still smaller group of cases represent extension of infection from adjacent organs such as perforated gastric or splenic flexure colonic carcinomas.

The solitary splenic abscess without sepsis in other organs and without evidence of a primary focus is rare, occurring in only 16 per cent of all cases of splenic abscess (9). These abscesses behave like subphrenic abscesses and may rupture into the pleural cavity (8) as well as into the peritoneal cavity. Rupture causing general peritonitis is exceedingly rare. The usual clinical findings are systemic toxicity, abdominal tenderness and rigidity and cardiovascular collapse.

The diagnosis of the unruptured splenic abscess is a difficult one, mimicking a subphrenic or perinephric abscess. The position of the abscess in the spleen determines the symptomatology. In the upper pole, the signs are of subdiaphragmatic irritation with left chest pain, left shoulder pain and occasionally left pleural effusion and fixation of the left diaphragm. In the lower pole, one may feel an enlarged spleen which is tender with signs of peritoneal irritation in the left upper quadrant of the abdomen. A friction rub may be heard over the spleen. Frequently, as in the first case, the abscess may be asymptomatic.

Occasionally, what appears to be a left subphrenic abscess is drained and a septic course persists from what proves to be an associated splenic abscess. Subsequent splenectomy is then curative. Ochsner and Graves (10) reported a 2.4 per cent incidence of this association in 3,000 subphrenic abscesses. Radiographic study of the left upper quadrant frequently demonstrates enlargement of the spleen with displacement of the stomach medially and depression of the splenic flexure of the colon in a caudal direction. Single, or more often, multiple gas filled pockets within the splenic parenchyma demonstrated radiographically, although rare, are quite characteristic of splenic abscess or at least splenic infarction with parenchymal necrosis. This gas formation has been demonstrated in the absence of culturable bacteria.

The treatment of splenic abscess should be surgical. Procrastination in the surgical treatment of splenic abscess is usually due to uncertainty as to the diagnosis; however, when the diagnosis is made, treatment should not be delayed. The complications of perforation into the serous cavities and/or septicemia are much too serious to condone delay. The results of treatment with antibiotics alone, although often modifying and containing the infection to some extent, are not curative.

Most cases should undergo splenectomy, the indications being a ruptured abscess, multiple abscesses within the spleen, an upper pole abscess or associated hemorrhage. Occasionally, in the very ill patient with a lower pole abscess, splenotomy and drainage alone may be carried out. The high mortality figures in the older literature for splenectomy in these circumstances led many surgeons of that period to favor splenotomy (9). The advances in modern surgery have altered this practice. The marked improvement in the patient's general condition on control of the vascular pedicle noted both by Whelan (7)

and in our case suggests that this should be the first step in the surgical approach to the spleen and that splenectomy should follow. Although the thoracoabdominal approach would enhance the technical ease with which the diffusely adherent spleen can be removed, we feel that this is contraindicated for fear of contamination of the pleural cavity.

Wide drainage of the left subphrenic space should be carried out. We have been dissatisfied with the results of simple tube or Penrose drainage and have instituted sump drainage with continuous irrigation of the left subphrenic space with sterile saline solution. Beginning in the immediate postoperative period, this has eliminated clogging of the drainage tract and tubes by fibrino-purulent material and has produced a much more effective cleansing and drainage of the subphrenic space.

Because of the high incidence of associated distant sites of infection, the use of antibiotics in adequate dosage and based on culture and sensitivity reports is important even when a splenic abscess is removed completely.

#### SUMMARY

Two cases of splenic abscess, the first presenting as acute peritonitis due to rupture of the abscess into the peritoneal cavity and the second with secondary infection of a splenic infarction associated with sickle cell anemia are presented. Both patients, critically ill, were treated with splenectomy and recovered. This is the second reported survivor of a ruptured splenic abscess. The suppuration may occur in the spleen secondary to splenic infarction, mycotic emboli, traumatic hematomas or as the result of direct extension from infected neighboring organs. The complications of splenic abscess are catastrophic and the condition should be treated by splenectomy upon confirmation of the diagnosis. An occasional lower pole abscess in a very poor risk patient may be treated by splenotomy and drainage. Ancillary antibiotic therapy and adequate drainage are important for securing a satisfactory outcome.

#### REFERENCES

1. Whelan, Thomas J.: Abscess of the spleen. *Am. J. Surg.*, 94: 945, 1957.
2. Inlow, W. D.: Traumatic Abscess of the Spleen. *Ann. Surg.*, 85: 368, 1927.
3. McSherry, C. K. and Dineen, P.: The Significance of Splenic Abscess. *Am. J. Surg.*, 103: 618, 1962.
4. Kennedy, J. H. and Harvey, C. A.: Ruptured Splenic Abscess: An Unusual Cause of Acute Abdominal Disease. *West. J. Surg.*, 69: 151, 1961.
5. Cockshatt, W. P. and Weaver, E. J. M.: Primary Tropical Splenic Abscess: A Misnomer. *Brit. J. Surg.*, 49: 665, 1962.
6. Billings, A. E.: Abscess of the Spleen. *Ann. Surg.*, 88: 416, 1928.
7. Davidson, S. G., Doig, J. A., and Everhard, G. J. H.: Acute Splenic Abscess. *J. Roy. Coll. Surg. Edinb.* 6: 44, 1960.
8. Lang, P. R. and James, C. F.: Abscess of the Spleen with Diaphragmatic Perforation. *Virginia M. Monthly*, 72: 26, 1945.
9. Walker, I. J.: Abscess of the Spleen. *New England J. Med.*, 203: 1025, 1930.

10. Ochsner, A. and Graves, A. M.: Subphrenic Abscess: Analysis of 3,372 Collected and Personal Cases. *Ann. Surg.*, 98: 961, 1933.
11. Chaffee, J. S., Lasher, R. L., and Tredway, J. B.: Splenic Abscess: Report of 4 Cases. *Ann. Surg.*, 148: 979, 1958.
12. Reid, S. E. and Lang, S. J.: Abscess of the Spleen. *Am. J. Surg.*, 88: 912, 1954.

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## CLINICO-PATHOLOGICAL CONFERENCE

### Progressive Weakness in a Middle Aged Male

*Edited by*

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A fifty-one year old negro male entered the Mount Sinai Hospital because of progressive weakness of one year's duration. He was hospitalized nine months earlier at another hospital with weakness of the arms and legs and migratory polyarthrititis involving the large joints. The patient lost thirty-five pounds in three months and also noted palpitations and dyspnea on exertion. He did not drink alcoholic beverages but smoked approximately twenty cigarettes a day. Physical examination at that time revealed a slow and slurred speech and striking muscle wasting about the hips and shoulders. There was paresis of the orbicularis oculi muscles and all the proximal muscles including those in the neck. No fasciculations, muscle tenderness or fatigue phenomena were noted. The reflexes were intact and the sensory examination was normal. Rales were heard in the left lung base in addition to bilateral wheezes. The hemoglobin was 11.5 gm per cent, the erythrocyte sedimentation rate 74 mm per hour, and the white blood count 9900 cu mm with a normal differential count. The urine, blood sugar, blood urea nitrogen and uric acid were normal. Electrophoresis of the serum showed a normal pattern. The serum calcium was 8.2 mg per cent, phosphorous 5.1 mg per cent, and the alkaline phosphatase activity 1.7 Bodansky units. A Kveim test was negative. Electromyographic studies yielded non-specific abnormalities. An electrocardiogram showed premature ventricular contractions, runs of paroxysmal supraventricular tachycardia and an intra-atrial block. A chest x-ray showed extensive diffuse interstitial fibrosis of the right lung and portions of the left. X-ray examination of the skull, bones and kidneys were normal. An upper gastrointestinal series showed dilatation of the proximal small bowel. Scattered focal atrophy and degeneration of the muscle fibers with some fibrosis were seen in a muscle biopsy and multiple non-caseating epithelioid granulomas with giant cells were present in a lymph node biopsy specimen. A biopsy specimen of the liver was normal and a bronchial biopsy specimen showed thickening of the basement membrane and squamous metaplasia. The patient was given prednisone, testosterone, digoxin, isoniazid and pyridoxine. He was discharged improved. At home, he became progressively weaker, even having difficulty getting out of a chair, and was admitted to the Mount Sinai Hospital. He denied headaches, visual disturbances, numbness, paresthesias or loss of sphincteric function. The physical examination was unchanged except that his speech was more slurred. The urine, white blood cell count, serum electrolytes and liver function

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tests were normal. Thyroid uptake studies were normal; several LE preparations were negative, the antistreptolysin titer was not elevated and the latex fixation test was negative. The erythrocyte sedimentation rate was 30 mm per hour and the electroencephalogram was normal. Electron micrographic studies demonstrated abnormalities suggestive of a myopathy with nerve involvement. The spinal fluid pressure was 350 mm of water and contained 60 erythrocytes and 60 mononuclear cells per cubic millimeter. The spinal fluid sugar was 38 mg per cent and the protein 171 mg per cent. No improvement was noted in the patient's muscle strength after 6 mg of Tensilon. In spite of large doses of prednisone, the patient became weaker. X-ray examination of the right scapula showed a cystic lesion at its inferior border. Atrial fibrillation with ventricular rate of 140 per minute, poorly controlled by digoxin, developed. One week before death an electroencephalogram showed recurrent cycles of abnormal activity, consistent with diffuse cerebral dysfunction with focal abnormalities in the right temporal region. Several throat cultures grew *Candida albicans*. A lumbar puncture was performed and the fluid contained 169 leukocytes, 62 lymphocytes and 12 large cells, which were interpreted as histiocytes. Cultures were sterile. Despite supportive measures, the patient became comatose with increased respiratory difficulty and died on the 110th hospital day, two years after the onset of symptoms.

*Dr. Osserman:*\* The proximal muscle weakness and weight loss, in addition to speech involvement, suggest myasthenia gravis. There are a small group of myasthenic patients in which muscle atrophy occurs relatively early in the course of the disease and affects predominantly the proximal limb muscles. The patient presented with a wasting disease involving predominantly muscles. Before discussing the clinical possibilities, Dr. Khilnani will present the x-ray findings.

*Dr. Khilnani:*† The earliest chest examination showed an interstitial process predominantly in the bases of both lungs (Fig. 1). The infiltrations were streaky rather than nodular, but did not look lymphangitic in nature. Sarcoidosis is a possibility although it would be unusual since there was no adenopathy and the infiltrations were primarily at the bases. No obvious carcinoma or metastatic lesions were present. A barium meal examination showed good esophageal motility, and no evidence of scleroderma. The proximal small bowel was slightly dilated but the mucosa was normal. The intravenous pyelogram showed no obvious lesion in the kidney except for a localized collection of dye in the upper pole which appeared to represent a communicating cyst. There were at least three skeletal lesions. The lesion in the scapula was irregular in contour suggestive of a destructive lesion. A similar lesion was seen in the left anterior iliac spine (Fig. 2) and another in the shaft of the left humerus. The lesions were atypical for metastatic carcinoma. An unusual granulomatous lesion cannot be excluded.

*Dr. Osserman:* Certain facts in the protocol are very important; the onset of

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progressive weakness with marked weight loss, muscle atrophy involving particularly the proximal muscles, dyspnea on exertion and an x-ray picture of interstitial fibrosis.

The clinical course, the absence of thymic involvement, the lack of response to Tensilon and the finding of a non-caseating lymph node would make the diagnosis unlikely.

Myopathies occur in acromegaly, Addison's disease, Cushing's Disease, after prolonged steroid therapy, thyrotoxicosis, and aldosteronism due to low serum potassium. This patient did not have an endocrinopathy. It is interesting to note that in the thyrotoxic myopathy, we have never found a myasthenic re-

FIG. 1. X-ray of the chest revealing a fine interstitial process throughout both lungs, most marked at the bases. Multiple discoid atelectasis are also present in the left base.



sponse to Tensilon. On the other hand, about 53 per cent of our myasthenic patients without obvious signs of thyrotoxicosis have a definite hyperthyroidism.

We must also consider polyarteritis nodosa, vasculitis, disseminated lupus, rheumatoid arthritis, scleroderma, and polymyositis. There were no lupus erythematosus (LE) cells found, the ASLO titer and the C-reactive protein were normal. Furthermore, these diseases do not have a tendency to affect the proximal limb muscles. The absence of skin lesions and normal esophageal studies make scleroderma unlikely. The electromyographic changes are those seen in polymyositis, however, lymph node granulomas and pulmonary infiltrations would be unusual in polymyositis.

There is a form of dystrophy that involves the limb musculature but the electromyographic findings of nerve involvement do not fit this picture. Furthermore, the serum glutamic oxalacetic transaminase is generally elevated.

Let us now consider the differential diagnosis of granulomas. They are of

two types. I think we can dismiss the type caused by streptococcus, beryllium and tuberculosis. Although he was treated with isoniazid, he had no fever, and sputum and stomach cultures failed to grow acid fast organisms. The bone lesions were also atypical. Even though there may be meningeal and brain involvement from a tuberculoma, I think we can dismiss it as a possibility.

The malignant lymphomas, sarcoidosis and multiple myeloma have to be included in the differential diagnosis.

Non-caseating granuloma with giant cells are most commonly seen in sarcoidosis, but they also can occur in many of the lymphomas. Similar biopsies mixed motor and sensory lesions, and finally the cases from the Mayo Clinic,



FIG. 2. Irregular destructive lesion in the supra-acetabular area of the left iliac bone (arrows).

may be seen in Hodgkin's Disease but a definitive diagnosis cannot be made in the absence of Reed-Sternberg cells. Malignant lymphomas are associated with neuritis, neuropathy and myopathy which results mainly from pressure on structures with the brain and spinal cord. In Hodgkin's Disease, for instance, the dura is frequently involved and impinges on adjacent structures. However, because of their mode of spread, both motor and sensory abnormalities occur.

Carcinomatous myopathy has been of great interest to me because abnormalities occur in the nervous system and the muscles unrelated to metastasis. Denny-Brown was the first to report two cases with motor and sensory involvement. Pathologically, they showed degeneration of the dorsal spinal nerves and a polymyositis of the muscles. He noted that histologically the lesions looked very much like Vitamin E, pyridoxine or pantothenic acid deficiency. Subsequently, a number of cases were reported with cerebral dysfunction, of a condition called "Eaton" disease. Eaton reported a patient with an oat

cell carcinoma of the lung, who presented with marked muscular weakness and a picture that one might see in myasthenia gravis. Electromyographic studies were consistent with a neuromuscular block and a few responded partially to Tensilon and Prostigmin. Dr. Lambert is able to differentiate these patients from true myasthenics because very slow electrical stimulations caused a typical myasthenic fall-off pattern in the EMG; whereas, with stimulation at fifty per second facilitation occurs and results in improvement in muscle action potentials. The differentiation is not only electromyographic but there is definite clinical evidence of facilitation since the patient's strength improves after exercise. This improvement is only transient because with repeated exercise neuromuscle block will occur. Therefore, we must consider carcinoma of the lung. Indeed, it would not have to be carcinoma of the oat cell type because there have been similar cases reported with ovarian, prostatic, and breast carcinomas. Again, the proximal muscles and the limb muscles are involved and at times they have ptosis and even bulbar paralysis.

The electromyogram and the clinical picture does not resemble myasthenia and I strongly consider carcinoma of the prostate. Finally, I think sarcoidosis is the major disease to be considered. Sarcoidosis presents with fatigue, malaise, and frequently weight loss. Previously, it was considered a dermatological disease, but we are now well aware of its systemic nature.

I saw a woman with combined sarcoidosis and myasthenia about five years ago. She was admitted for fever of unknown etiology, a high eosinophilic count, proximal muscle weakness and a positive Tensilon test. A skin and muscle biopsy was consistent with sarcoidosis. In addition, she was hyperthyroid. However, at no time did her lungs show the typical changes of sarcoidosis, such as fibrosis or hilar adenopathy.

Mayock (3) collected 1250 patients and tabulated organ involvement. The lungs are involved in over 90 per cent of the cases. Bone was involved up to 25 per cent of the time. Polyarthrititis is also very common and occurs in 10 per cent of the cases. Muscles are not frequently involved (only 2.3 per cent in his group). In the case mentioned, we were able to make the diagnosis of a sarcoidosis based on the muscle biopsy. The patient under discussion had non-caseating granulomas, but muscle biopsies showed no evidence of a sarcoid lesion. The nervous system is involved in 16 per cent of the cases and cardiac involvement with atrial fibrillation and blocks have been reported.

The liver and spleen are frequently affected although a positive liver biopsy is usually associated with a high serum alkaline phosphatase activity. Both were normal in this case. The Kveim test is almost always positive, but in the acute fulminating cases, it may be positive in only 50 per cent of the cases. Therefore, a negative Kveim test does not rule out sarcoidosis. Patients with sarcoidosis will also frequently have a positive Wasserman and a colloidal gold reaction.

Tuberculosis in the course of sarcoidosis occurred in about 4 per cent of Mayo's series. Five cases were the pulmonary type but one was meningeal. Since sarcoidosis is usually a slow progressive disease and the death rate is low,

only 3½ per cent were due to sarcoidosis per se. This patient had both progressive muscular atrophy and central nervous system dysfunction in addition to the other manifestations I have mentioned. I would, therefore, suggest that he had Beck's sarcoid and a space occupying lesion of the brain which may be lymphoma or a metastatic carcinoma.

*Question:* How would you explain the bone lesions?

*Dr. Osserman:* Sixteen per cent of sarcoid patients have bone lesions. Although they usually are of a different type, punched out lesions do occur.

*Dr. Rubin:\** The original scalene lymph node biopsy showed non-caseating epithelioid granulomas. In areas of the lymph node there was an eosinophilic hyalin-like material, so-called para-amyloid, which is found in sarcoidosis. The muscle biopsy showed atrophy of muscle fibers, interstitial infiltration with lymphocytes and fibrosis. A connective tissue stain clearly demonstrated fibrosis of muscle (Fig. 3) and collections of histiocytes, which represent response to muscle necrosis rather than myositis. The cells which were found in the spinal fluid, had small irregular nuclei and were interpreted as histiocytes (Fig. 4).

At autopsy, both lungs were enlarged and air was present in the pleural spaces. The right lung weighed 680 grams and the left 580 grams. Section of the lungs after inflation with formalin displayed small cystic areas, more marked at the periphery of the lung (Fig. 5). Alveolar structures were replaced by a uniform, firm tissue, which microscopically was interstitial fibrosis (Fig. 6). Some metaplastic changes were also found in the epithelium. In some areas, the structure of the lungs was not well maintained and there was collapse of pulmonary tissue with replacement by dense fibrous tissue. Multinucleated giant cells were found lying free in alveoli and represented metaplasia of alveolar histiocytes. Pneumonia was also present, which may have been the cause of death.

The giant cells were not found in the interstitial tissue or in the areas of fibrosis, but only in alveolar spaces. Rare fibrosing granulomas were also found in the interstitial tissue of the lung. In some areas of the lung which were not fibrotic, emphysema was present. At this point, I would say that we must consider sarcoidosis as a strong possibility in view of the lymph node granulomas, the interstitial fibrosis, and the granulomas within the lung.

However, in the alveolar spaces of some areas of the lung were clumps of cells with bizarre nuclei and clear material within their cytoplasm, *i.e.* signet ring cells (Fig. 7).

Signet ring cells were present in alveolar or lymphatic spaces, but not within the fibrotic septa. Well formed glands were found in the lung but metastatic adenocarcinoma was found in the jejunum and within the cerebellum. Carcinoma involved the brain and infiltrated the lateral ventricle, impinging upon the ventricular space. The meninges of the spinal cord were infiltrated, but the substance of the spinal cord was not involved. An abdominal lymph node contained a fibrosing granuloma as well as metastatic carcinoma (Fig. 8). Deep

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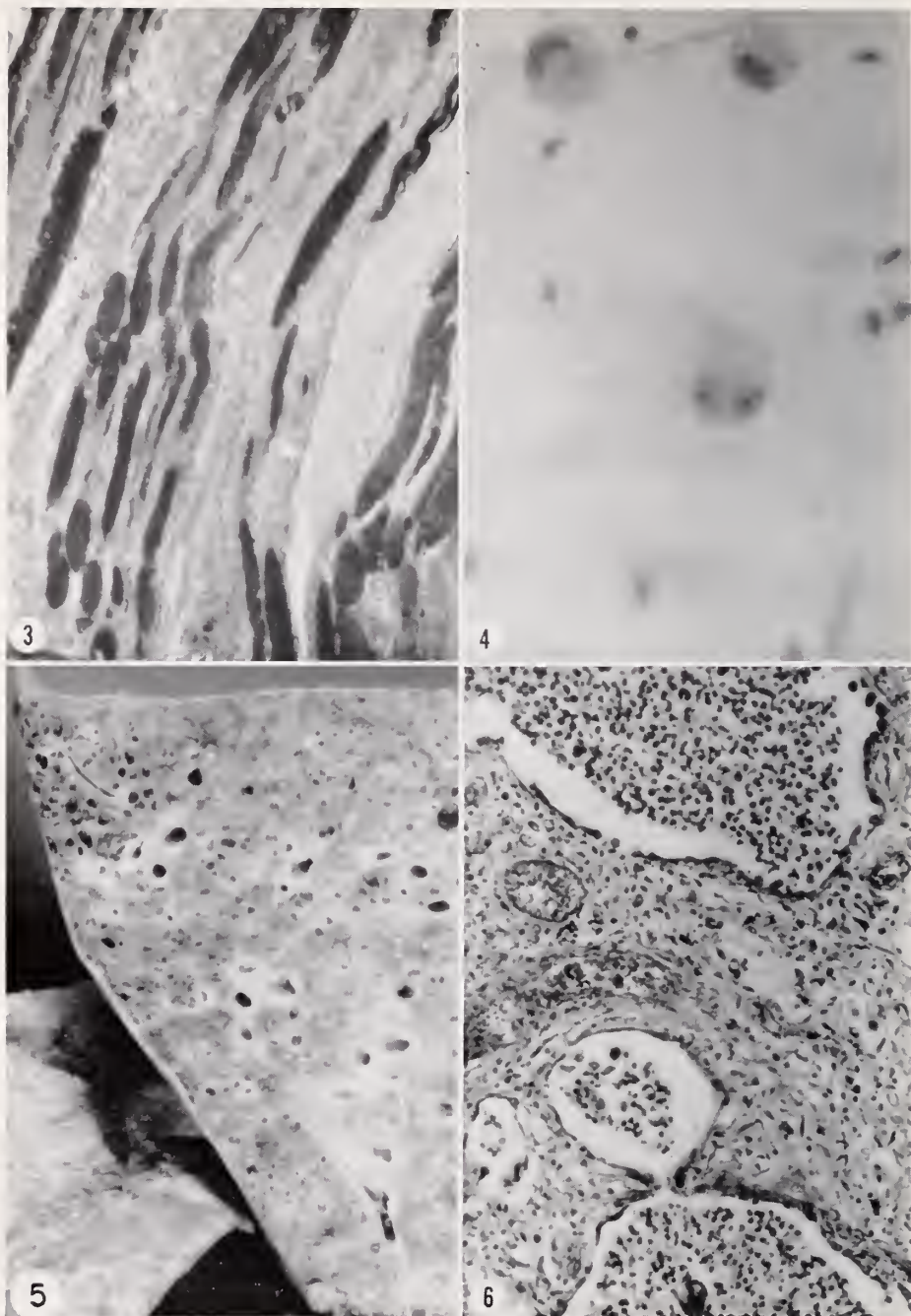


FIG. 3. Muscle biopsy showing diffuse fibrosis (Trichrome  $\times 150$ ).

FIG. 4. Histiocytes within the spinal fluid (H & E  $\times 800$ ).

FIG. 5. Section of lung with diffuse microcystic changes.

FIG. 6. Interstitial fibrosis of the lung (Reticulum stain  $\times 150$ ).



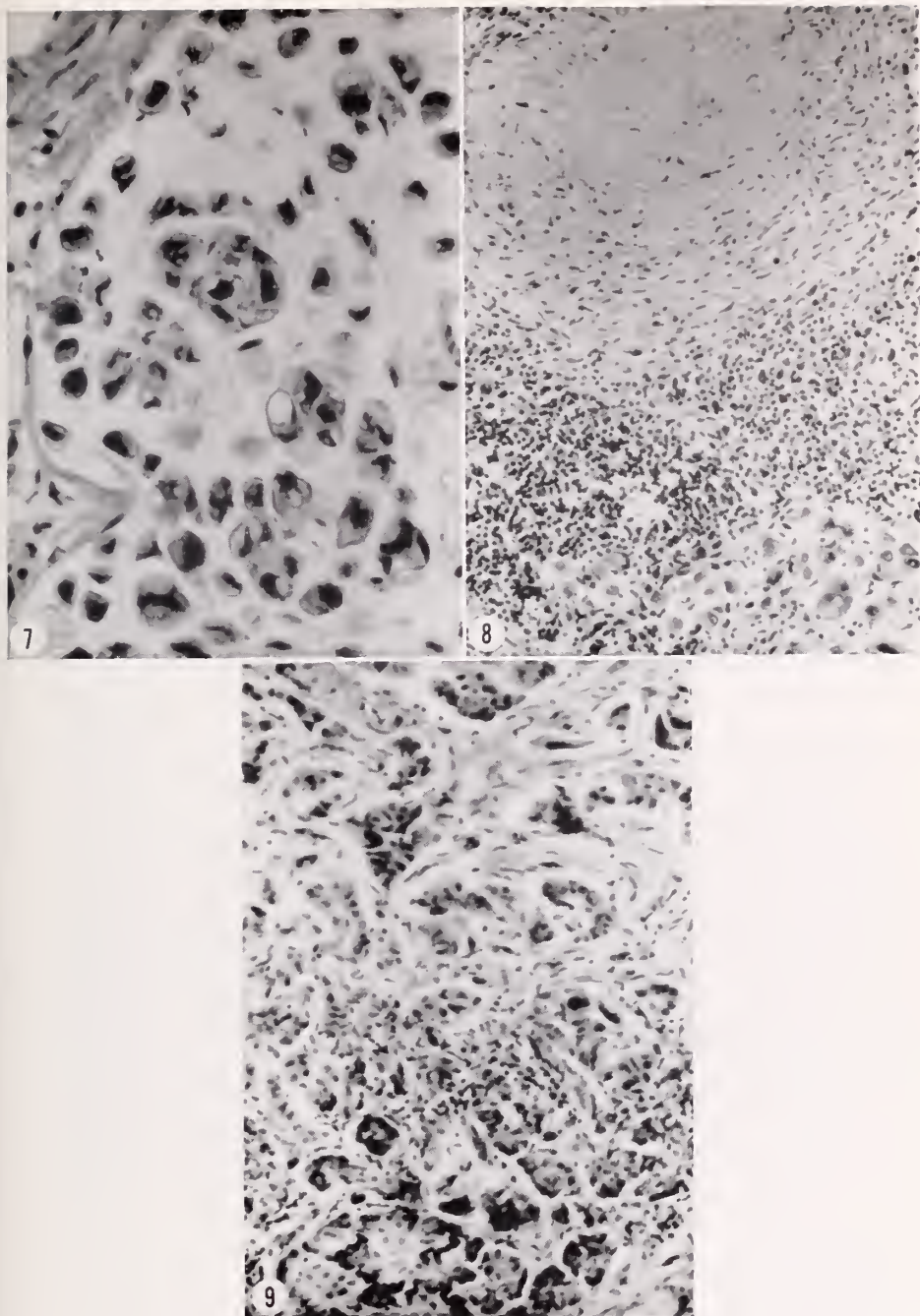


FIG. 7. Signet ring cells within the alveolar spaces (H & E  $\times 400$ ).

FIG. 8. Lymph node showing a fibrosing granuloma and carcinoma cells (H & E  $\times 150$ ).

FIG. 9. Adenocarcinoma of the pancreas (H & E  $\times 200$ ).

within the pancreas and not evident from the outer surface was a small adenocarcinoma—the primary tumor (Fig. 9).

Carcinomatous myopathy, interstitial fibrosis of the lung and non-caseating epithelioid granulomas—It is known that carcinoma may be associated with neuro-myopathic syndromes. Brain (4) has divided them into three categories. The first and the third types are primarily neurological, but his second category is a myopathy frequently associated with a myasthenic syndrome and atrophy of muscle. This particular type of myopathy occurs occasionally in a pure motor form, as in this case. Degeneration of ganglion cells and demyelination do not occur and response to the anticholinergic drugs is variable. However, the nature of this association remains speculative. One could postulate an immunologic reaction to toxic products from the tumor, or a common virus as a cause of both the tumor and the neuromyopathy (1). They occur more frequently with carcinoma than with the reticulososes or lymphomas, although they have been associated with many types of tumor. The granulomas in the lymph nodes, the interstitial fibrosis and granulomas in the lungs were compatible with sarcoidosis. However, no other organs were involved. There are sarcoid-like lesions associated with carcinoma. They were first described in 1911 by Wolbach and subsequently many tumors have been associated with sarcoid-like lesions in the lymph nodes, which are morphologically indistinguishable from sarcoidosis. The presence of carcinoma and granulomas in the same lymph node is uncommon but has been reported several times. Usually the lymph nodes which show these changes are topographically related to the tumor. In carcinoma of the lung the scalene nodes are frequently affected; and in carcinoma of the liver the portal lymph nodes are involved. One should be careful about diagnosing a scalene node as sarcoidosis on the basis of biopsy in the absence of systemic manifestations of sarcoidosis. What about sarcoidosis itself and neurologic manifestations? Silverstein et al (5) reported a number of cases of sarcoidosis which showed a motor pattern of neuropathy and in one of their cases, a muscle biopsy showed atrophic changes. We are then left with several possibilities: 1) carcinomatous neuromyopathy, associated with sarcoid-like lesions; 2) sarcoidosis associated with myopathy secondary and interstitial pulmonary fibrosis; and 3) carcinomatous neuromyopathy with sarcoid-like lesions and an interstitial pulmonary fibrosis of unknown etiology. I believe that the patient suffered from carcinomatous neuromyopathy and doubt that he had sarcoidosis. I believe that the interstitial fibrosis was idiopathic. However, the possibility that he had two diseases—sarcoidosis and carcinoma, cannot absolutely be ruled out on morphologic grounds.

#### FINAL DIAGNOSIS

1. Adenocarcinoma of the pancreas with metastases to the brain, meninges, lung and lymph nodes
2. Carcinomatous myopathy with muscular atrophy
3. Sarcoid-like reaction secondary to carcinoma
4. Diffuse interstitial pulmonary fibrosis

## REFERENCES

1. Denny-Brown: Primary Sensory Neuropathy with Muscular Changes Associated with Carcinoma. *J. Neurol. Neurosurg. & Psychiat.*, 11: 73, 1948.
2. Eaton, L. M., and Lambert, E. H.: Electromyography and electric stimulation of nerves in diseases of motor unit. *J.A.M.A.*, 163: 1117, 1957.
3. Mayock, R. L., Bertrand, P., Morrison, C. E., and Scott, J. H.: Manifestations of Sarcoidosis, Analysis of 145 Patients with a review of nine series from the literature. *Am. J. Med.* 35: 67, 1963.
4. Brain, R., and Henson, R. A.: Neurological Syndromes Associated with Carcinoma. The Carcinomatous Neuromyopathies. *Lancet*, 275: 971, 1958.
5. Silverstein, A., Feuer, M., and Siltzbach, L.: Neurologic Sarcoidosis. *Arch. Neurol.*, 12: 1, 1965.

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## RADIOLOGICAL NOTES

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### CASE NO. 262

A 24 year old female was transferred to the hospital from another institution for treatment of lumbar vertebral fractures. In the course of an automobile accident which occurred two weeks prior to admission the patient sustained fractures of the bodies of L2, L3, and L4, and pedicular fractures of L2 with slight forward dislocation of L2 on L3. There was no significant neurologic deficit. A seat belt was worn during the accident.

Two weeks following admission the patient began to vomit and physical examination revealed upper abdominal distension. Routine blood count was normal. X-ray examination of the abdomen showed evidence of partial mechanical high jejunal obstruction (Fig. 1). Barium meal examination was performed two days later and confirmed a partial mechanical obstruction of the upper jejunum, less marked than on the original plain film study (Fig. 2). Satisfactory decompression was accomplished with a Cantor tube but signs and symptoms recurred two weeks later. Diagnoses of intramural hemorrhage with stenosis or jejunal perforation with adhesions and stenosis were entertained and exploratory laparotomy carried out. At laparotomy, a small jejunal perforation with localized abscess formation and adhesions was found 12 to 18 inches distal to the ligament of Treitz. The localized perforation was closed and the adhesions lysed. The post-operative course was uneventful.

### DISCUSSION

See discussion following Case No. 263.

*Case Report:* TRAUMATIC RUPTURE OF THE JEJUNUM OCCURRING WITH THE USE OF A SEAT BELT.

### ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Mansho T. Khilnani, The Mount Sinai Hospital, New York, N.Y.

### CASE NO. 263

A 19 year old female was admitted to the hospital complaining of abdominal pain following an automobile accident. A seat belt was worn during the accident. Examination revealed a hematoma in the right mid-abdominal wall at the level of the umbilicus. There was marked spasm and rigidity over the mid and upper abdomen.

Plain film study of the abdomen in multiple projections was performed six hours after the accident (Fig. 1). A mild inhibition ileus was noted and there

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Case 262, Fig. 1. Supine film of the abdomen reveals a few widely dilated loops of jejunum in the mid and upper abdomen seen against a background of generalized gaseous distension of the bowel. The superior plates of the vertebral bodies of L2, L3 and L4 show irregularity due to fracture. Fracture of the pedicles of L2 is also present, but not well demonstrated.

were functional changes in the cecal contours. A small collection of gas bubbles was present to the left of the spine at the level of L3, but not observed at this time. There was no free intraperitoneal air.

Exploratory laparotomy was performed. There was a hematoma in the omentum and the transverse mesocolon. There were contusions of the liver. A greenish discoloration of the tissues was seen in the right paracolic gutter, but a collection of fluid was not encountered on incision of the peritoneum here. The duodenum was not explored. The abdomen was drained and closed.

Two days later, the patient was febrile, dyspneic and toxic. Chest x-ray





Case 262, Fig. 2. Barium meal examination performed two days later again reveals a few dilated jejunal loops, less marked than that seen in Fig. 1. Barium traverses the dilated loops indicating an incomplete obstruction. The site of obstruction is not precisely located.

revealed consolidation or atelectasis of the right upper lobe, pneumonic infiltrations in the right lower lobe, and right pleural exudate. Plain film study of the abdomen revealed marked adynamic ileus and a mass with gas bubbles in the right flank which displaced the right colon medially. Gas bubbles were also observed in the paraspinal region. Intravenous urogram showed medial displacement of the right ureter (Fig. 2). Barium enema examination showed marked displacement of the right colon and severe functional changes (Fig. 3).

The patient was again explored surgically. A large abscess was drained through the right flank. The abdomen was then opened through a separate incision and peritoneal exudate and fluid were observed. The entire small



Case 263, Fig. 1. Plain film study of the abdomen performed six hours after automobile accident reveals a mild inhibition ileus of a non-specific nature. There is a small collection of gas bubbles in the left paraspinal retroperitoneal tissues (arrow A). There are functional changes in the contour of the cecum (arrow B). There was no free intraperitoneal air.

bowel was traced. When the duodenum was uncovered, a wide rupture was found at the junction of the second and third portions on the inferior aspect. There was an associated rent in the small bowel mesentery. The duodenal rupture was closed primarily and the abdomen drained and closed.



Case 263, Fig. 2. Intravenous urogram performed two days later reveals a large soft tissue mass in the right flank which contains gas bubbles. The right ureter is displaced medially.

The patient's subsequent course was stormy. The duodenal closure broke down and a fistula developed and drained through the right flank. A drainage tube was inserted into the duodenum via the fistulous tract. A feeding jejunostomy was performed. Pulmonary infection and heavy bronchial secretions required bronchoscopic intervention. Sudden gastrointestinal hemorrhage occurred at one point requiring massive transfusion therapy. A specific site of bleeding could not be determined at laparotomy, but the bleeding



Case 263, Fig. 3. Barium enema examination following the intravenous urogram reveals marked displacement of the right colon and severe functional changes in this portion of the bowel. Residual opaque material in the urinary tract is seen.

ceased spontaneously. The duodenal fistula drained heavily at first but drainage gradually diminished. The feeding jejunostomy and duodenal drainage tube were eventually removed.

Barium meal examination was performed seven weeks after admission (Fig. 4). The duodenal fistula at the junction of the second and third portions was demonstrated and seen to communicate with a cavity in the right lower quadrant lateral to the cecum, as well as with the right flank. The cavity in the right lower quadrant was explored and drained. Duodenal drainage





Case 263, Fig. 4. Barium meal examination performed seven weeks after admission shows slight dilatation of the second portion of the duodenum. Opaque material drains from the duodenal fistula at the junction of the second and third portions towards the right flank (along arrows) and into a cavity adjacent to the cecum in the right lower quadrant (arrow A).

diminished further and finally ceased altogether. A final barium meal examination confirmed the duodenal closure without obstruction.

#### DISCUSSION

Safety experts agree that seat belts increase the wearer's chances of surviving an automobile accident and reduce the incidence of major injuries. However, it has become evident that some injuries can be directly attributed to the seat belt itself. When the seat belt is properly applied, it should cross the



lower abdomen and bear on both sides of the pelvis near the anterior superior iliac spines. If a severe force is generated, the pelvis bears the strain and may actually be fractured (1). Of greater interest is the result of improper seat belt application. There is a tendency to cinch the belt across the mid or upper abdomen and bear on the lower ribs or flanks rather than the pelvis. In this case, the abdomen itself absorbs the force of impact and severe intra-abdominal injury may result. In Case No. 263, the hematoma of the abdominal wall to the right of the midline at the level of the umbilicus is the telltale mark of improper belt application, as has been pointed out by previous authors (1, 2, 3, 4). The details in Case No. 262 as regards belt application and the condition of the abdominal wall on admission are not available. Parenthetically, a lap-shoulder device has been advocated as an improvement in belt design which might avert this type of abdominal injury (3, 4, 5).

The various possible mechanisms of injury in ruptured bowel due to blunt abdominal trauma have been analyzed and evaluated (6, 7, 8, 9). As regards the duodenum, Cocke and Meyer (6) list three possible mechanisms: crush against the vertebra, shearing or tangential force applied to the duodenum in its relatively fixed retroperitoneal location, and a closed loop mechanism. The latter mechanism requires a gas filled duodenum, a closed pylorus and a contracted fibromuscular ligament of Treitz with an acutely flexed duodenal-jejunal junction. They found no anatomical evidence supporting the first two mechanisms in their material (48 collected cases) and suggest the closed loop mechanism as the most important as regards duodenal injury. In Case No. 263, however, the rent in the mesentery found adjacent to the duodenal rupture suggests that the tangential or shearing mechanism may have operated in this case. As regards the small bowel, Williams and Sargent (8) present ingenious experimental evidence in support of compression against the vertebral column as the most important mechanism of injury. The spinal injuries in Case No. 262 and the near-midline location of the perforation support this thesis.

Almost all duodenal ruptures are retroperitoneal in location. Initial roentgen signs most often are bubbles or other collections of air in the retroperitoneal tissues, extending to the perirenal and psoas regions, below the diaphragms, up into the mediastinum and even into the neck (7). A small percentage of cases may show free air (6). Intramural hematoma may occur rather than perforation (10) and the possibility of delayed rupture must also be borne in mind (6). Complications include fistula, bowel obstruction, abscess and pancreatic injury. Mortality and morbidity increase sharply when there is failure to recognize the perforation at the time of initial surgery. (7, 11).

In jejunal and ileal perforations, free intraperitoneal air is of course the roentgen hallmark. However, delayed perforation, or walled off perforation, abscess formation, adhesions and obstruction may also occur, as illustrated by Case No. 262.

*Case Report:* TRAUMATIC RUPTURE OF THE DUODENUM OCCURRING WITH THE USE OF A SEAT BELT.

## REFERENCES

1. Garrett, J. W., and Braumstein, P. W.: The Seat Belt Syndrome. *J. Trauma*, 2: 220, 1962.
2. Fish, J., and Wright, R. II.: The Seat Belt Syndrome—Does It Exist? *J. Trauma*, 5: 746, 1965.
3. Tolins, S. H.: An Unusual Injury Due To The Seat Belt. *J. Trauma*, 4: 397, 1964.
4. Cocks, W. M., Jr., and Meyer, K. K.: Splenic Rupture Due To Improper Placement Of Automobile Safety Belt. *J. A. M. A.*, 183: 693, 1963.
5. Campbell, H. E.: The Automobile Seat Belt and Abdominal Injury. *Surg. Gynec. & Obst.*, 119: 591, 1964.
6. Cocks, W. M., Jr., and Meyer, K. K.: Retroperitoneal Duodenal Rupture: Proposed Mechanism, Review of Literature, and Report of a Case. *Am. J. Surg.*, 108: 834, 1964.
7. Gould, R. J., and Thorworth, W. T.: Retroperitoneal Rupture of the Duodenum Due to Blunt Non-penetrating Abdominal Trauma. *Radiology*, 80: 743, 1963.
8. Williams, R. D., and Sargent, F. T.: The Mechanism of Intestinal Injury in Trauma. *J. Trauma*, 3: 288, 1963.
9. Jordan, J. S. and McAfee, D. K.: Wounds of the Jejunum and Ileum. *Am. Surgeon*, 29: 630, 1963.
10. Hill, M. C.: Roentgen Diagnosis of Duodenal Injuries. *Am. J. Roentgenol.*, 94: 356, 1965.
11. Burrus, G. R., Howell, J. F., and Jordan, G. L.: Traumatic Duodenal Injuries: An Analysis of 86 Cases. *J. Trauma*, 1: 96, 1961.

## CASE NO. 264

A 6 year old boy was admitted to the hospital for an elective right nephrectomy. Four months prior to admission he was admitted to another institution following a fall from a tree. A fracture of the left wrist was diagnosed but in addition the patient complained of pain in the left flank. Gross hematuria was present and a diagnosis of contusion of the left kidney was advanced. Intravenous urogram revealed no abnormality on the left but a marked hydronephrosis was seen on the right. Hematuria ceased on conservative therapy. Previous history was entirely non-contributory.

On admission, routine blood count, urinalysis and BUN were normal. Blood pressure of 118/80 was recorded. Intravenous urogram was performed. A film made 3 minutes after injection (Fig. 1) revealed some opaque material in markedly dilated internal collecting structures of the right kidney. A very fine smooth line of increased density rimmed the dilated structures in many areas. The line could still be seen on a film made 8 minutes after injection. A film made 20 minutes after injection (Fig. 2) revealed complete filling of the markedly dilated internal collecting system. The fine line was no longer seen. The thickness of the renal cortex could be identified in many areas and measured approximately 4 to 5 mm. The right ureter was never filled. The left kidney showed no gross abnormality. A fine regular rippling to the mucosa of the left renal pelvis was noted. The diagnosis was advanced of right ureteropelvic obstruction and proximal hydronephrosis.

Right nephrectomy was performed. No unusual anatomy was noted about the renal hilum. Gross pathological examination showed hydronephrosis with

smooth epithelial surfaces except near the ureteropelvic junction where there were some vertical striations to the mucosal folds. The junction itself was quite narrow but a probe passed easily. No gross valves were seen. Histologic examination of longitudinal sections made through the ureteropelvic junction revealed a somewhat corrugated surface with microscopic valve-like projections. Histologic examination of sections of the renal cortex showed overall



Case 264, Fig. 1. Abdominal film made 3 minutes after the injection of opaque material reveals some opacification of the markedly dilated right internal collecting system. A very smooth line of increased density rims the dilated structures in many areas (along arrows). A finely rippled appearance to the mucosa in the left renal pelvis can barely be seen, but the left side is otherwise normal.

thinning but the glomeruli and tubules were well preserved. There was no evidence of inflammation or scarring.

The patient made an uneventful recovery. The blood pressure remained at approximately 120/80 until the fourth post-operative day when it was recorded as 106/66.

#### DISCUSSION

Various observers have previously reported examples of the "crescent sign," a thin rim of increased density seen during intravenous urography which outlines a hydronephrotic sac (1, 2, 3, 4). In the previously reported cases, it would



Case 264, Fig. 2. Abdominal film made 20 minutes after the injection of opaque material reveals dense and complete opacification of the hydronephrotic right internal collecting system. The ureter is not visualized.

appear as if the crescent represents a nephrogram of the entire residual thickness of the markedly attenuated renal cortex. In the case presented, the exquisitely thin crescent is contrasted with the measurable 4 to 5 mm thickness of the cortex. This appearance rather suggests a relationship to the fine rim of



opaque material which surrounds a benign renal cyst frequently seen during nephrotomography. The anatomical basis is a thin layer of compressed and reoriented renal collecting tubules. A relatively large quantity of injected opaque material is probably essential for its demonstration. (The exact quantity of opaque material injected was not documented in this case but was most likely 20 to 25 cc.)

The demonstration of microscopic mucosal valves with longitudinal sections taken through the ureteropelvic junction has previously been reported in cases of congenital ureteropelvic obstruction (5). Whether or not they represent the anatomical basis for the obstruction is not determined.

The rippled appearance to the mucosa of the left renal pelvis is a finding said to be associated with infection. However, there is no evidence for infection in this case and the finding is therefore presumed to represent an anatomical variation.

The significance of the blood pressure elevation in this case is also not determined.

*Case Report:* CONGENITAL UNILATERAL HYDRONEPHROSIS DUE TO URETEROPELVIC OBSTRUCTION AND AN UNUSUAL "CRESCENT SIGN."

#### ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Florian Yandel, Good Samaritan Hospital, Suffern, New York.

#### REFERENCES

1. Dunbar, J. S., Norgrady, M. B. and MacEwan, D. W.: The Crescent Sign—A Pyelographic Sign of Severe Hydronephrosis. Presented at the Sixty-third Annual Meeting of the American Roentgen Ray Society, Washington, D. C., Oct. 2-5, 1962.
2. Allen, R. P., Condon, V. R., and Collins, R. E.: Multilocular Cystic Hydronephrosis Secondary to Congenital (Ureteropelvic Junction) Obstruction. An Adjunct to Diagnosis with Intravenous Urography. *Radiology*, 80: 203, 1963.
3. LeVine, M., Allen, A., Stein, J. L., and Schwartz, S.: The Crescent Sign. *Radiology*, 81: 971, 1963.
4. Greenberg, E. I., and Rabinowitz, J. G.: Radiological Notes, Case No. 211, Congenital Unilateral Hydronephrosis in the Newborn. *J. Mt. Sinai Hosp.*, 30: 366, 1963.
5. Lich, R., Jr.: The Obstructed Ureteropelvic Junction. *Radiology*, 68: 237, 1957.

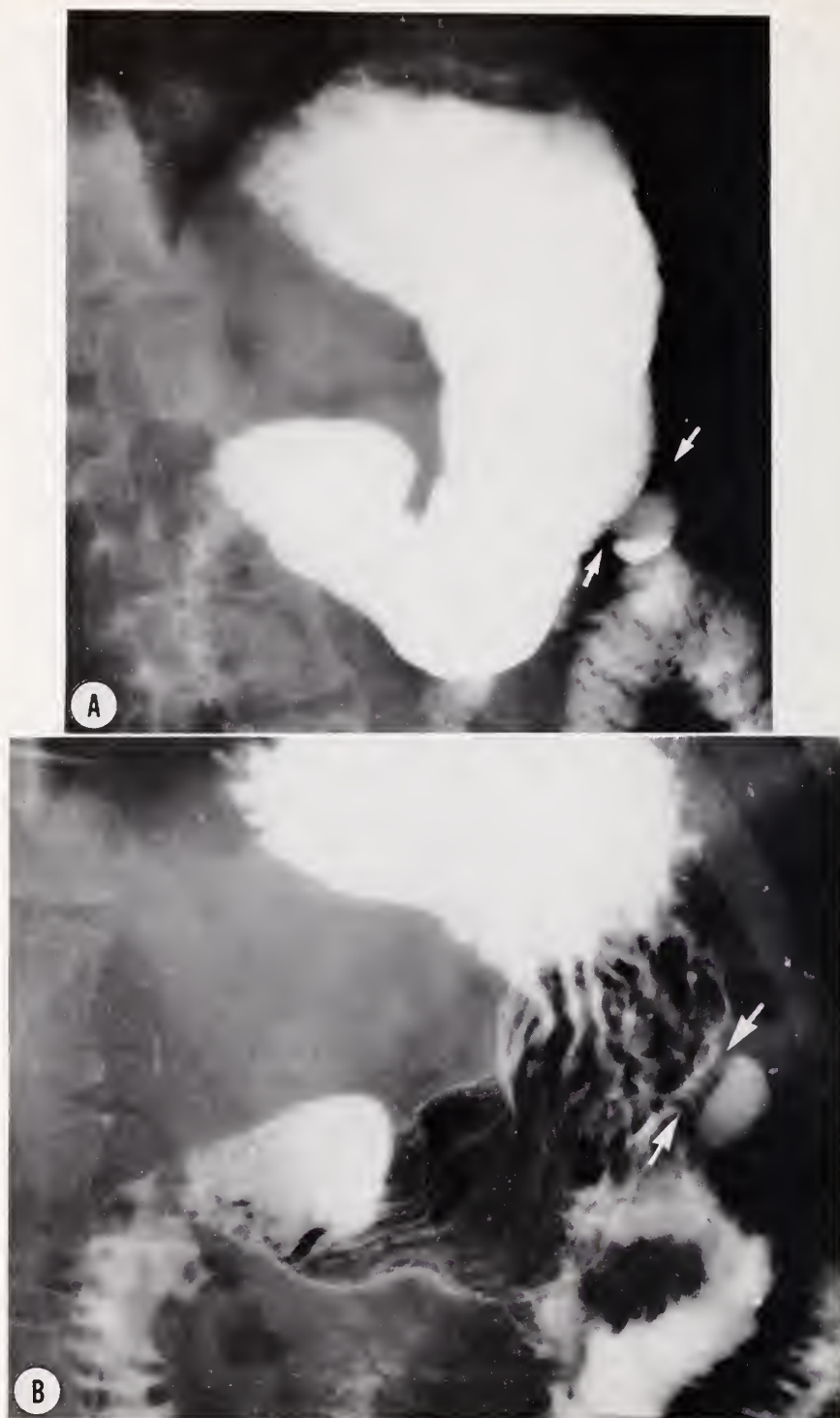
#### CASE NO. 265

A 58 year old male was admitted to the hospital with a one week history of dysphasia, retrosternal discomfort and heartburn. There was no associated nausea or vomiting. No anorexia or weight loss were noted.

Physical examination was non-contributory, and the laboratory studies were normal.

Barium meal examination revealed a small hiatus hernia with no regurgitation or esophagitis. There was a 3 by 1½ cm diameter, mushroom-shaped diverticulum arising from the mid portion of the greater curvature along its vertical segment (Figs. 1A and B). The neck of the diverticulum measured 1 cm in





Case 265, Fig. 1

diameter (between arrows). It filled and emptied well, and there was no evidence of retained material within the diverticulum. Some increased secretions were seen in the upright position with layering of fluid above the barium column. No ulcerations were noted within the diverticulum. The remainder of the stomach appeared normal.

#### DISCUSSION

Gastric diverticula are most commonly noted near the cardia, high up in the posterior aspect of the lesser curvature of the stomach. They are rarely larger than 3 cm in size and are almost always asymptomatic. On occasion, retained secretions and food particles can be seen within them. Few well substantiated cases have been described with ulcerations and hemorrhage. Most of the diverticula of the stomach are thought to be of a congenital type, so called true diverticula, with all muscle layers included within their wall. Review of the literature states that only very few gastric diverticula are ever found along the greater curvature, and no x-ray demonstrations of any of the cases were noted in review of the recent literature. In the above case, the hiatus hernia was probably responsible for the patient's symptoms, and the diverticulum was of incidental significance.

The differential diagnosis of all gastric diverticula rests with ulcerations of the stomach. In order to diagnose a diverticulum, one must outline a distinct neck within which one can distinguish regular folds continuous with the rugal pattern. The outlines of the body of the diverticulum are smooth and the out-pouching usually fills and empties during the course of the examination. With an ulcer on the other hand, the gastric folds stop at the neck and do not enter the niche. The ulcer is often slightly irregular in contour with amorphous barium filling it. The ulcer does not show any intrinsic ability to fill and empty. Often considerable spasm is noted in the region of the gastric ulcer.

*Case Report:* GASTRIC DIVERTICULUM ALONG THE GREATER CURVATURE.

#### ACKNOWLEDGMENT

The editors wish to thank Dr. H. Weinrauch for permission to publish this case.

#### REFERENCES

1. Bockus, H. L., *Gastroenterology*, 2d ed. (Philadelphia, 1963), I, 893.
2. Templeton, F. E., *X-ray Examination of the Stomach* 2d ed. (Chicago, 1964), p. 534.

Case 265, Fig. 1A. There is a 3 by 1½ cm mushroom-shaped diverticulum along the greater curvature of the stomach. This is well seen in this upright right anterior oblique view where there is also some layering of fluid and air above the barium level. The diverticulum is noted to fill and empty quickly. No solid material is noted within the diverticulum. The neck of the diverticulum is noted to measure about 1 cm in diameter (between arrows).

Case 265, Fig. 1B. Examination in the left posterior oblique projection reveals air outlining the gastric folds within the neck of the diverticulum (between arrows). Air rises into the diverticulum which is noted to be situated relatively anteriorly along the greater curvature.

## CASE NO. 266

A 25 year old female was admitted to the hospital with a 24 hour history of severe upper epigastric pain and vomiting. The patient had noted a temperature elevation for three days before admission. There was no accompanying jaundice, anorexia or weight loss. Previous to this acute episode, the patient had no gastrointestinal symptoms and felt entirely well.

Physical examination revealed an acutely ill patient complaining of severe upper epigastric pain which was aggravated by deep breathing. There was tenderness and guarding in the right upper quadrant. Temperature was 101°F. There was no evidence of scleral icterus.

Examination of the abdomen revealed a firm, globular, slightly tender smooth mass extending from the mid costal margin on the left side to the mid clavicular line on the right side. In order to rule out the possibility of acute cholecystitis or hydrops of the gallbladder, an intravenous cholangiogram was performed which revealed the following: the gallbladder was seen to fill moderately well and revealed no gross abnormalities; the intrahepatic ducts (Fig. 1A) were normal in caliber and displaced downward and to the right (upper arrows); the inferior portion of the common bile duct was also displaced downward and laterally by a mass in the mid portion of the liver (lower arrows Fig. 1B).

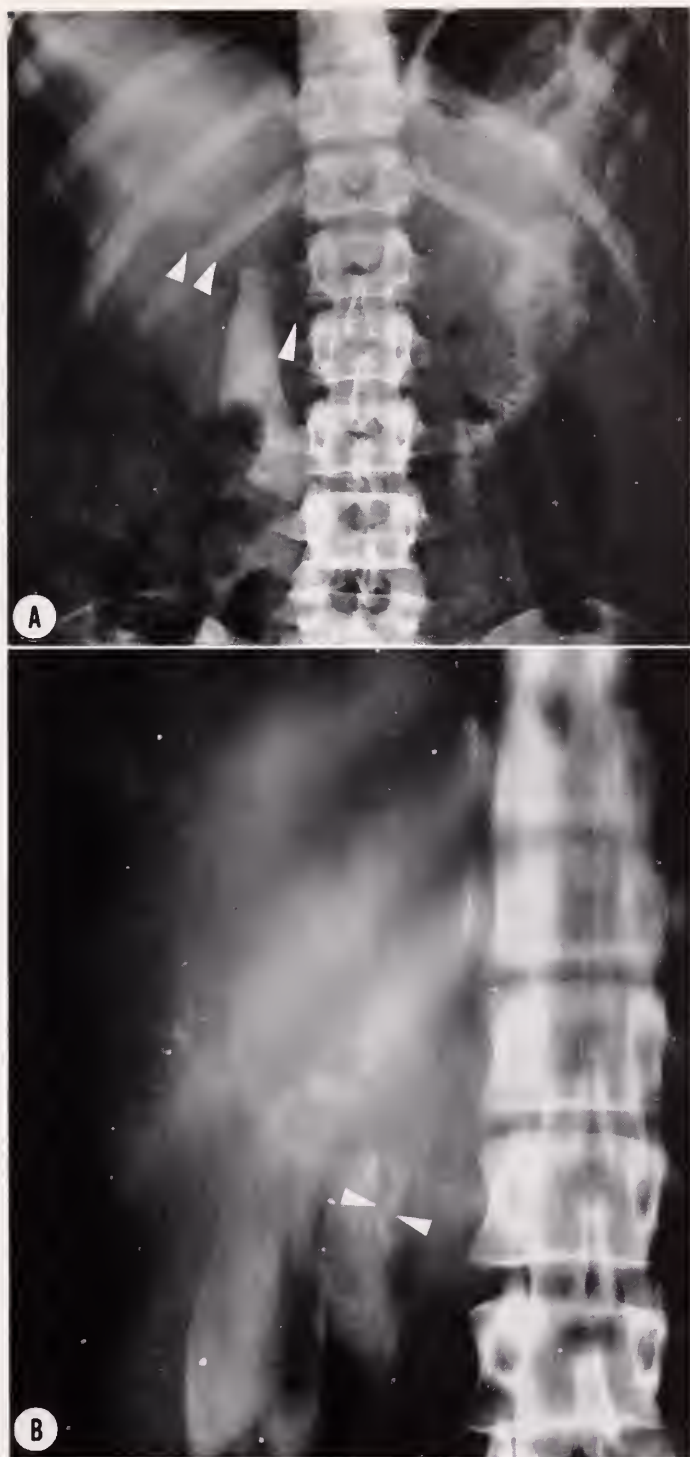
Because of the finding of the mass and the acute febrile illness, laparotomy was performed to rule out the possibility of a liver abscess. An upper paramedian incision extending into a right anterior thoracotomy approach was performed. This revealed a 20 cm in diameter highly vascular mass occupying the right lobe of the liver. Needle biopsy produced a large amount of necrotic yellow-green material which, on frozen section, was noted to be a hepatoma. Because of this and the absence of other pathology, a partial hepatectomy was performed with removal of 60 to 65 percent of the right lobe of the liver. Permanent histologic sections confirmed the presence of a hepatoma. The patient tolerated the surgery well and was noted to have no complaint in the postoperative period.

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Case 266, Fig. 1A. Antero-posterior view of the abdomen during the course of intravenous cholangiography reveals the gallbladder to be moderately well filled with contrast medium. It is normal in size and position.

The intrahepatic bile ducts are displaced downward and to the right (along upper arrows) by a mass situated in the mid portion of the liver above and to the left of these ducts. The distal portion of the common bile duct is also displaced downwards (lower arrow) by the above described mass.

Case 266, Fig. 1B. Tomographic section in the frontal projection reveals the distal inch of the common bile duct to be normal in position as it traverses the intramural portion of the duodenum (between arrows). The more proximal portions of the common bile duct as well as the intrahepatic duct are again seen to be displaced downwards and to the left by the mass within the liver.



Case 266, Fig. 1

## DISCUSSION

This case is presented in order to demonstrate the value of careful scrutinization of the distribution of the intrahepatic ducts when performing intravenous cholangiography. There was an obvious extrinsic displacement of the intrahepatic branches by a mass in the mid portion of the liver (Figs. 1A and B). The lowermost portion of the common bile duct was normal in course and caliber as it entered the wall of the duodenum, but its upper portion was also displaced by the mass. This implied a large hepatic mass with some compression at the porta hepatis. Similar displacements of intrahepatic structures are well known when performing splenoportogram, but have rarely been described in intravenous cholangiography.

*Case Report:* HEPATOMA DEMONSTRATED BY DISPLACEMENT OF BILIARY DUCTS DURING INTRAVENOUS CHOLANGIOGRAPHY.

*Received for publication April 15, 1966.*



## ULCERATIVE AND GRANULOMATOUS COLITIS: A FOREWORD

This exhaustive study and detailed illustration of the radiographic features of the major inflammatory disorders of the colon by Drs. Marshak and Lindner will, I believe, contribute enormously to our sorting out of this baffling group of diseases.

Although the modern study of the non-specific colonic inflammation of unknown origin was initiated more than a hundred years ago, no group of illnesses still requires more sorting out. Samuel Wilks of Guy's Hospital gave in 1859 the first modern description of ulcerative colitis: "I think, then, we must not use the term colitis, as some do, as synonymous with dysentery; the latter being, in fact, only one variety of colitis. . . . There are cases probably, however, of simple idiopathic colitis, though rare, and which may, indeed, be examples of acute dysentery; but such, in the absence of those peculiar features which are supposed to characterize that disease, can hardly receive the name; thus, for example, we have seen a case attended by discharge of mucus and blood where, after death, the whole internal surface of colon presented a highly vascular, soft, red surface, covered with tenacious mucus or adherent lymph, and here and there a few minute points of ulceration; and the coats, also, much swollen by exudation into the mucous and submucous tissues" (1). Moxon added to this description in 1875, "In other examples there has been extensive ulceration, commencing in the follicles, and spreading from them to destroy the tissue around, thus producing a ragged ulcerated surface" (2).

The other strand which the present authors have been disentangling from *ulcerative colitis* is the intriguing one of *granulomatous colitis*; the emergence of the latter as a separate entity is a recent story. The physicians of this hospital have long been interested in this curious type of inflammatory reaction of the bowel. Indeed, two years after Drs. Crohn, Ginzburg and Oppenheimer described their first patients with regional ileitis (3), Colp reported in 1934 "a case of non-specific granuloma of the terminal ileum and cecum" (4). Descriptions of involvement of all areas of the small bowel by this pathologic process followed rapidly, but it was not until 1952 that Wells (5) emphasized that the colon alone could be the seat of a similar process. While Marshak in 1956 (6) and Brooke in 1959 (7) called attention to the colonic aspects of granulomatous enteritis, the great surge of modern interest dates from the papers of Lockhart-Mummery and Morson (8) who wrote on "regional enteritis of the large intestine and its distinction from ulcerative colitis."

To this distinction the present study with its wealth of radiologic detail and pathologic correlation lends great weight. The dispassionate observer must conclude, pending the discovery of their etiologic agents, that these two disorders of the colon are distinct, but he would add that there probably exist other entities which need sorting out as well. It may be both interesting and salutary for the reader to be reminded that Wilks and Moxon were aware of the granulomatous variety of inflammation of the intestine. They wrote, "We have met

several times with severe local acute ileitis in the shape of a thickening of the whole of the coats, including the valvulae conniventes which stood out stiffly, while the whole wall was thick with inflammatory lymph, the microscope showing a generalized charging of the whole tissue with pyroid corpuscles. This condition was found in a circumscribed patch of from six inches to two or three feet" (9)\*. It is thus appropriate that Drs. Marshak and Lindner should have contrasted so vividly these separated entities.

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#### REFERENCES

1. Wilks, S.: Lectures on Pathological Anatomy delivered at Guy's Hospital during the Summer Session of 1857-58, London: Longman, Brown, Green, Longmans and Roberts, 1859.
2. Wilks, S., and Moxon, W.: Lecture on Pathological Anatomy, ed 2, London: J & A Churchill, 1875, pp 408-409.
3. Crohn, B. B., Ginzburg, L., and Oppenheimer, G. D.: Regional Ileitis: A Pathologic and Clinical Entity, J.A.M.A., 99: 1323, 1932.
4. Colp, R.: A Case of Non-Specific Granuloma of the Terminal Ileum and Cecum, Surg. Clin. N. Amer., 14: 443, 1934.
5. Wells, C.: Ulcerative Colitis and Crohn's Disease, Ann. Roy. Coll. Surgeons England, 11: 105, 1952.
6. Marshak, R. H., and Eliasoph, J.: Non-Specific Ileocolitis, Acta Radiologica Interamericana, 6: 24, 1956.
7. Brooke, B. N.: Granulomatous Diseases of the Intestine, Lancet, 2: 745, 1959.
8. Lockhart-Mummery, H. E., and Morson, B. C.: Crohn's Disease (Regional Enteritis) of the Large Intestine and its Distinction from Ulcerative Colitis, Gut, 1: 87, 1960.
9. Wilks, S., and Moxon, W.: *loc cit*, p 406.

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\*I am indebted to Dr. George Burton, Upjohn Fellow in Gastroenterology, The Mount Sinai Hospital, for this reference.



## Ulcerative and Granulomatous Colitis

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For many years the finding of nonspecific inflammatory disease of the large bowel was equivalent to a diagnosis of ulcerative colitis. In recent years it has become apparent that the granulomatous process, which in the small bowel is known as regional enteritis, can also involve the colon. Thus the differential diagnosis of nonspecific inflammation of the colon rests between ulcerative and granulomatous colitis. The etiology of both diseases remains unknown. As a rule it is possible to distinguish the two entities on the basis of their clinical, roentgen and pathological characteristics, but at times features are mixed or intermediate and it is not possible to make a clear-cut distinction by present criteria. In such cases further observation will usually clarify this diagnosis. When a definite diagnosis cannot be made, we prefer to classify the case for the time being, "Colitis, type unknown," with a description of the salient features rather than to force the case into either category or to add intermediate classifications. Although some common etiology may in time become apparent, it seems to us that ulcerative and granulomatous disease represent distinct entities and that subsequent investigation will more likely be advanced by maintaining the two groups separate than by attempting to unify them.

### ULCERATIVE COLITIS

Characteristic findings in patients with ulcerative colitis are fever, abdominal cramps and diarrhea with blood in the stool. At times constipation rather than diarrhea may occur. In many patients the onset is insidious with vague abdominal complaints and gradual change in the frequency and character of stools. In others the onset is abrupt with fever, abdominal pain and bloody diarrhea becoming rapidly more severe over a period of days or weeks. In a few patients the inception is explosive with high fever, systemic toxicity, severe diarrhea and electrolyte depletion or hemorrhage. Gross blood in the stool is characteristic and may precede the onset of diarrhea. Perianal fistulas and anorectal disease occur in some patients with ulcerative colitis, but they are not characteristic findings. Extracolonic manifestations, including arthritis, uveitis and such skin changes as erythema nodosum or pyoderma gangrenosum may occur. Ulcerative colitis as a rule involves the rectum, even when the rest of the colon is spared; thus sigmoidoscopy can be expected to provide positive diagnostic findings of granularity, friability and ulceration with blood and exudate in the lumen. Toxic dilatation of the colon and free perforation into the

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peritoneal cavity are dread complications of ulcerative colitis. Carcinoma of the colon is a not infrequent sequel to chronic ulcerative colitis.

The course of ulcerative colitis is variable. In some patients with mild disease the clinical and sigmoidoscopic findings subside. In most patients, however, the disease becomes chronic with periodic clinical exacerbations and remissions. Medical treatment includes dietary manipulations, antispasmodics, antidiarrheal agents, blood transfusions, insoluble sulfa drugs, Azulfidine and corticosteroids;



FIG. 1. Universal ulcerative colitis. Entire colon is spastic and irritable. Contour of bowel is hazy due to an inflammatory exudate. Small indistinct ulcers extend from contour of transverse colon. The left side is incompletely filled (simulating a string sign) due to marked spasm accompanying the inflammatory process.

FIG. 2. Same case as Fig. 1, after evacuation. Mucosal folds are hazy and thickened in a symmetrical fashion. In contrast to granulomatous colitis, there is no evidence of nodularity or irregularity of the contour.

teroids; all of these are useful in managing symptoms and perhaps in inducing remissions, but there is no convincing evidence thus far that medical treatment alters the natural history of the disease. About 20 to 30 per cent of the patients sick enough to be hospitalized are ultimately treated surgically with colectomy and either ileostomy or ileoproctostomy. In those not operated upon, the disease may become quiescent or burnt-out after years of intermittent activity.

On pathological examination the colon displays features of an exudative inflammation which involves primarily the mucosa, secondarily the submucosa and only occasionally the muscularis. The bowel wall is thin or of normal





FIG. 3. Universal ulcerative colitis. Right side of colon is so spastic and irritable that complete filling was not obtained. The folds are thickened, with tiny ulcerations extending from contour. Because of over-filling of left side of colon, the inflammatory process in this region can easily be missed.

FIG. 4. Same case as Fig. 3, after evacuation. Involvement of the entire colon is now better visualized. The folds are thickened throughout and maintain a symmetrical pattern. Extent of involvement in inflammatory disease is often best determined on the evacuation film.

thickness; however, edema, accumulation of fat and hypertrophy of muscle due to inflammation may create the impression of a thickened bowel. Ulcerations are shallow and coalesce, leaving islands of mucosa as irregular tags, called pseudopolyps. The classical form of ulcerative colitis involves the entire colon. Often, however, the process is segmental. In such cases, the rectum alone is usually involved or the entire left side of the bowel is diseased. Segmental forms of ulcerative colitis without disease of the rectum are uncommon. The diseased areas of bowel are continuous without intervening areas of normal



FIG. 5. Universal ulcerative colitis. Moderate degree of narrowing and rigidity associated with numerous inflammatory polyps and ulceration. The barium incidentally present in stomach was given by mouth.

bowel, and involvement of the gut wall is circumferential and symmetrical. In some cases of universal ulcerative colitis, the terminal ileum displays a superficial mucosal inflammation which is termed "backwash ileitis."

Histological examination of the colon confirms the exudative nature of the disease, with exudate and edema as prominent features which involve especially the mucosa. Occasional foreign body giant cells are noted, but granuloma systems are not identified. With time, fibrosis occurs within the bowel wall and the colon becomes distorted, rigid and shortened. The lumen narrows and strictures may form. Regional lymph nodes may be enlarged and on section show nonspecific inflammation.

*Roentgen Features of Ulcerative Colitis**Acute Stage*

The roentgen findings are secondary to three factors: edema, ulceration, and alterations in the motility of the bowel. There is a variable roentgen pattern, depending on whether the disease process is mild, moderate, or fulminant in

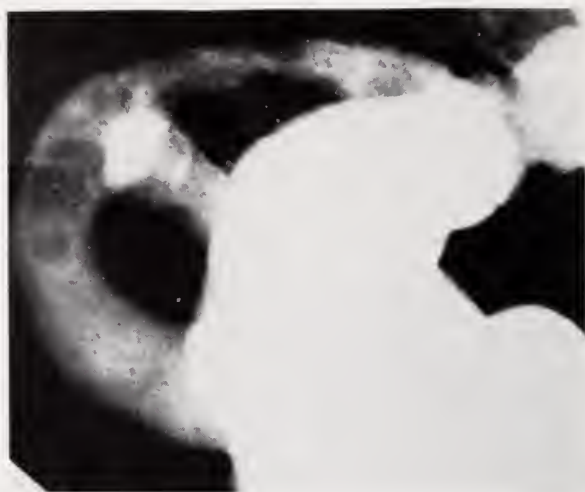


FIG. 6. Universal ulcerative colitis; spot film of sigmoid. Sigmoid is moderately narrowed and rigid. The barium has granular flocculant appearance due to admixture with blood, pus and mucus.



FIG. 7. Universal ulcerative colitis; spot film of distal transverse colon. There are numerous tiny, hazy, indistinct ulcerations along contour of bowel. Similar tiny flecks of barium are identified within lumen of the colon.

character. Inflammation produces motility changes characterized by spasm and irritability (Fig 1-4). Because of this spasm, narrowing and incomplete filling are frequent and in some areas the bowel is so attenuated that a "string sign" is simulated (Fig 1). Considerable secretions are present within the bowel lumen as a consequence of the edema, mucus, blood and exudate. The usual homoge-

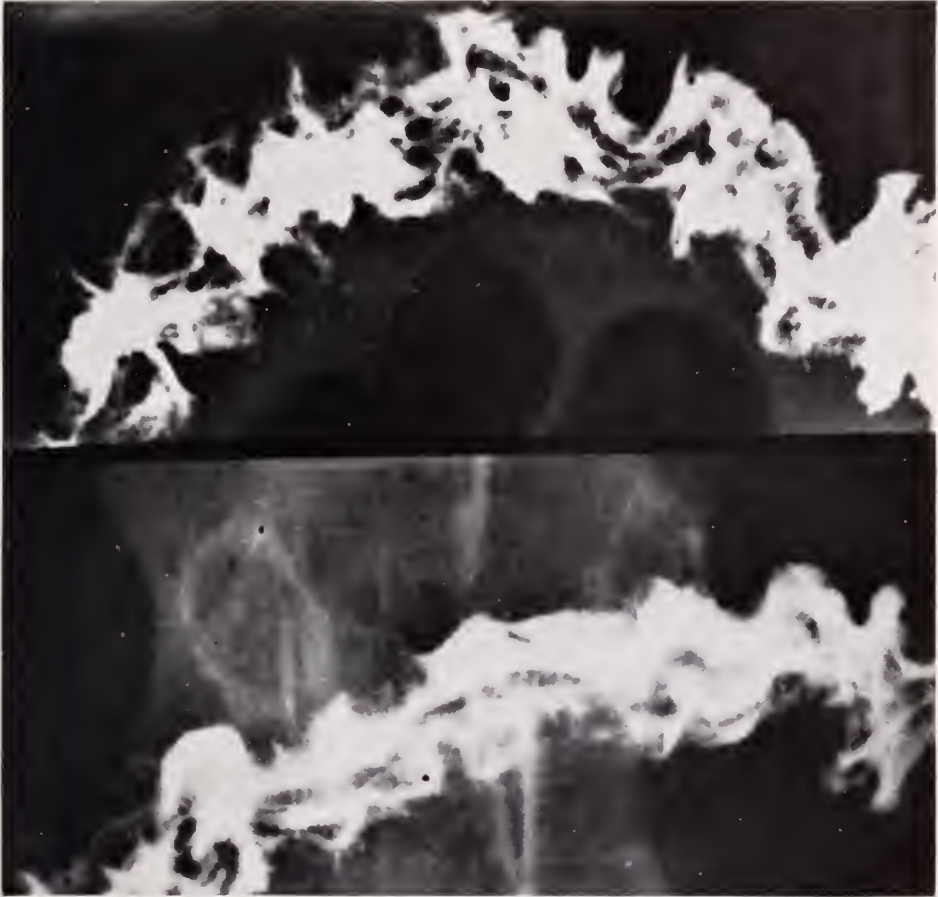


FIG. 8. Universal ulcerative colitis; spot film of transverse colon evacuation film. There is thickening, distortion, haziness of the mucosal folds and numerous tiny ulcerations. This type of ulceration is typical of ulcerative colitis.

neous-appearing barium mixture therefore has a granular, flocculant quality (Fig 6). Ulcerations are tiny and difficult to identify and are recognized either as serrations along the contour of the filled bowel (Fig 7) or after evacuation as small spicules extending from the mucosa (Fig 8). It should be noted, however, that serrations along the contour of the bowel may at times be seen normally, perhaps due to barium penetration in colonic glands. These are sharply defined and have a symmetrical, regular, uniform appearance (Fig 9). Ulcerations, in contrast, are hazy, less symmetrical and less uniform.



In the more acute or fulminant phase of this disease, the bowel contour appears obviously hazy. The fuzziness is due to excessive mucus and ulcerations. When the ulcerations are more marked (Fig 10A, 10B; 11A, 11B), the fuzziness is replaced by an irregular, serrated border, sometimes appearing as collar-button like projections as the ulcerations penetrate and become confluent. In



FIG. 9. Spicules, in a normal bowel. In an occasional normal patient, tiny spicules mimicking ulcerations are identified. Normal spicules are more symmetrical and sharply defined than ulcerations.

some cases the contours are grossly ragged and irregular. As ulceration proceeds, the edematous mucosa produces an appearance which has been called pseudopolyposis (Fig 5). Rarely localized pneumatosis coli may be recognized in an area of intense ulceration.

The mucosal pattern is best recognized on the evacuation film. The folds are thickened, hazy and associated with increased secretions. The pattern is regular and symmetrical and appears coarsely reticular (Fig 2, 4, 8, 11A, 11B).



Frequently numerous tiny, indistinct ulcerations projecting from the thickened folds are identified. When these projections have a very symmetrical and uniform appearance, the possibility that they are also due to a mixture of barium and mucus should be considered. When the edema is more prominent, the mucosal folds become swollen and show a coarsely granular appearance. The

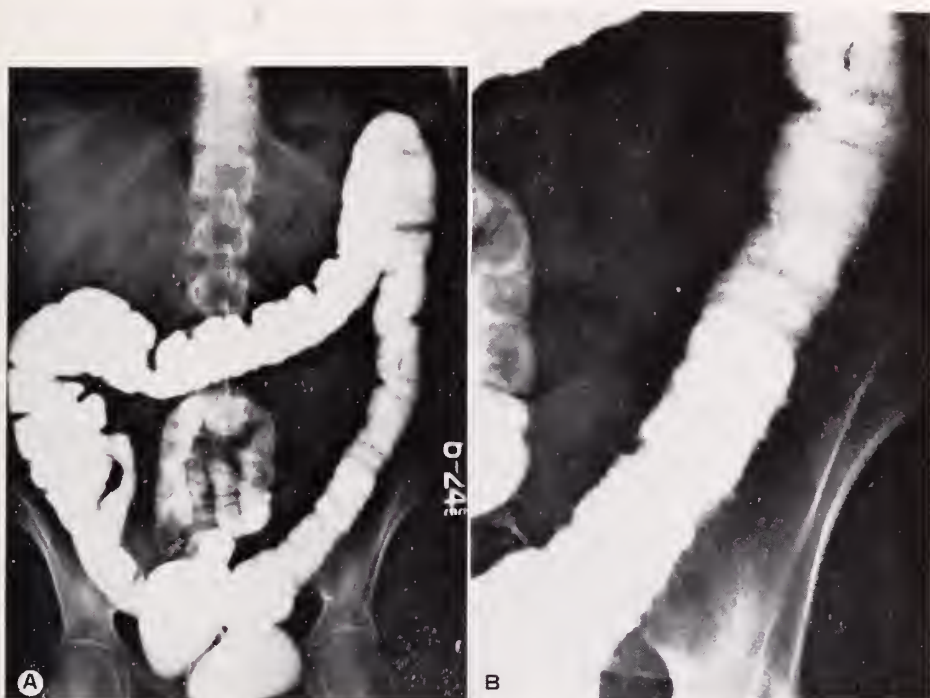


FIG. 10A. Universal ulcerative colitis with backwash ileitis. Minimal degree of narrowing and rigidity of entire large bowel associated with absent and irregular haustral markings. There is a distinct fuzziness along the contours of the descending colon and transverse colon because of numerous tiny ulcerations. Terminal ileum is slightly narrowed and rigid secondary to backwash ileitis.

FIG. 10B. Same case as Fig. 10A, spot film of descending colon. The fuzziness of the contour of bowel is again seen. Some of the ulcerations appear as collar-button projections.

edematous and inflamed mucosa forms symmetrical defects along the contour, which have been referred to as thumb printing (Fig 12).

### *Subacute Stage*

In the subacute stage, further roentgen features supervene due to continued ulcerations, beginning fibrosis, and mucosal regeneration. The mucosa assumes a more nodular appearance and the polypoid pattern becomes more prominent. The inflammatory polyps are usually small and uniform in appearance (Fig 5, 13, 14, 15). They may, however, be large, scattered and irregular. Tiny radio-lucent defects which appear comma-shaped between the larger polypoid lesions

are probably due to the pedicles. Areas of more intense ulceration produce marked irregularity of the contours which simulate a neoplasm, especially when distributed over a short segment. As a rule, the symmetrical appearance described previously is maintained. In minimal cases the haustral pattern may be unaffected. More often the haustra are distorted and irregular and are associated with some degree of rigidity. In the subacute stage these findings become more evident because of the continuing inflammatory process and the more marked narrowing of the lumen due to rigidity.

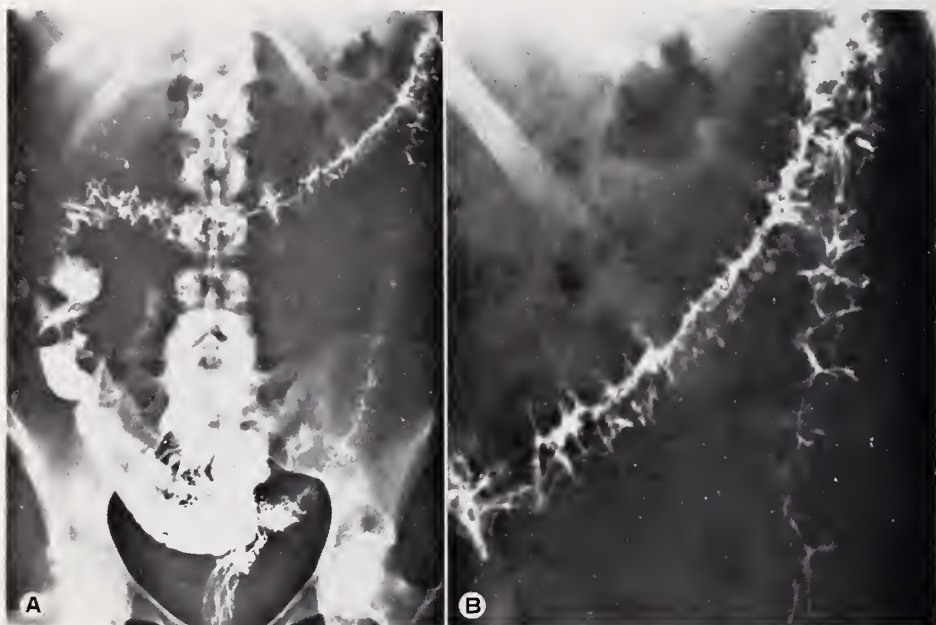


FIG. 11A. Same case as Fig. 10A, postevacuation. Mucosa throughout the bowel is thickened. There is more narrowing and rigidity of terminal ileum than is usually seen in backwash ileitis.

FIG. 11B. Same case as Fig. 10A, spot film of splenic flexure. Symmetrical thickening of mucosal folds associated with numerous tiny ulcerations.

Sinus tracts or fistulae are not a feature of ulcerative colitis but are common in granulomatous colitis.

### *Chronic stage*

In the chronic stage, fibrosis, epithelial regeneration, and pseudopolypoidosis are the prominent features (Fig 16 A and B). The result is a shortening of the bowel, depression of the flexures, narrowing of the bowel lumen and rigidity. Again, symmetry of involvement is conspicuous. The contours are relatively smooth due to fibrosis and healing of the ulcerations. The haustra are absent and the bowel has a tubular, rigid appearance. The flexures may be so contracted that a carcinoma is simulated. At this stage of the disease the roentgen

appearance usually remains fixed and unvarying despite clinical exacerbation or remission. The mucosa reveals a marked degree of atrophy with evidence of re-epithelialization. When roentgenograms are made at serial intervals during the course of the disease, one is astonished at the degree of shortening of the colon in the chronic stage of ulcerative colitis. It is remarkable that in a disease which is primarily mucosal cicatrization and contraction are so pronounced.

In some patients, in the chronic stage, the bowel remains fairly distensible



FIG. 12. Universal ulcerative colitis, evacuation film. Symmetrical thickening of the folds with multiple indentures along the contours which have been referred to as thumb printing. Granular quality of barium is due to admixture of blood, pus and mucus.

with little shortening and absent haustral markings with no evidence of a mucosal pattern. This appearance has been referred to as chronic, burnt-out ulcerative colitis (Fig 17).

An interesting feature in the diagnosis, especially of early or minimal ulcerative colitis, is the appearance of the descending colon. Normally this portion of the bowel may have no haustral pattern and because of spasm display features which can be confused with inflammatory changes. In the absence of obvious features of ulcerative colitis in other segments of the bowel a definite diagnosis of a lesion in the descending colon may be impossible.

Extension of ulcerative colitis with involvement of the entire colon can occur



from a process that is initially limited to one segment. However, patients with the disease confined to the rectum or left side of the colon may not show any evidence of involvement of the remainder of the colon despite repeated observations over a long period of time.

#### *Toxic Dilatation of the Colon*

One of the most dramatic and ominous episodes that may occur in the course of ulcerative colitis is the rapid development of striking colonic dilatation (1).



FIG. 13. Segmental subacute ulcerative colitis. Left side of the colon is involved with ulcerative colitis, characterized by a moderate degree of narrowing, rigidity and numerous small inflammatory polyps. The symmetrical involvement of the contours is identified. Despite repeated examinations over a period of many years there has been no extension of the inflammatory process.

This occurs in both acute and chronic phases of the disease and can be associated with extreme toxicity. A portion, or almost all, of the diseased colon becomes tremendously dilated. The distended, tender, silent abdomen suggests that the bowel is about to perforate. Pathological examination at this time shows marked dilatation and thinning of the colonic wall associated with ragged ulceration. Marked acute inflammatory changes are noted in all the coats of the colon associated with areas of necrosis. There is no evidence of organic obstruction in the toxic dilatation of ulcerative colitis. The exact mechanism responsible for the marked colonic distention is unknown.

In most of the cases of toxic dilatation, a simple film of the abdomen is diagnostic and a barium enema examination is unnecessary. In the anterior-posterior films of the abdomen taken with the patient lying on his back, the portion of colon most prominently distended is the transverse colon (Fig 18, 19). This is in part due to the fact that with the patient supine air in the column



FIG. 14. Universal ulcerative colitis. Rectum and sigmoid appear normal. Remainder of the bowel is involved with a moderately severe inflammatory process characterized by narrowing, rigidity, absent haustral markings, slight irregularity of the contour and numerous inflammatory polyps. On sigmoidoscopy, the rectum and lower sigmoid were minimally involved. Because of the normal roentgen appearance of the rectum and sigmoid there may be difficulty in the differentiation of this type of case from granulomatous colitis. Clinical features were those of ulcerative colitis.

rises to the highest segment. The distal descending colon and the sigmoid are less frequently distended. It is uncommon to find distention of the rectum, although the ulcerative process practically always involves this portion of the bowel. An erect or lateral decubitus view may be taken to exclude the presence of free air. Such films will also show fluid levels in the colon and it is fairly characteristic of this condition that the fluid levels are long and few in number. The caliber of the distended segments may be very great. A striking roentgen



feature is the fact that despite distention, the lengths of the visualized segments are relatively normal. The hepatic and splenic flexures are normally situated and identification of the visualized portion of the colon is not difficult. It is possible that the plastic exudate prevents the bowel from becoming elongated or contracted. The picture of marked distention associated with undistended or relatively narrowed portions of colon in between is in contrast to that seen in mechanical obstruction in which the colon proximal to the site of obstruction



FIG. 15. Universal ulcerative colitis, subacute stage. Entire colon is involved with an inflammatory process characterized by moderate degree of narrowing, rigidity, absent haustral markings and inflammatory polyps. Terminal ileum is normal.

is uniformly distended and frequently markedly redundant. The appearance of the bowel is diagnostic. In the segments involved the normal haustral pattern is absent (Fig 20 A and B). In less involved portions the haustra may appear thickened. Superimposed on the contour there may be innumerable broad-based nodular pseudopolypoid projections which extend into the lumen of the bowel (Fig 19, 21). Between the soft tissue projections air-filled crevices which in some instances have a serrated or tooth-like configuration may be identified. These presumably are the result of deep ulcerations. Peritonitis, at least of a localized nature, with plastic serosal exudate is usually present. There is no

evidence of fluid in the abdomen. The changes described above may develop in a very short period of time. When a free perforation occurs, air is readily identified under the diaphragm. It is not unusual in these cases for a considerable amount of air to accumulate under both leaves of the diaphragm and throughout the abdomen.

On occasion a barium enema examination is performed in these patients. Because of the high incidence of spontaneous perforation in toxic dilatation,

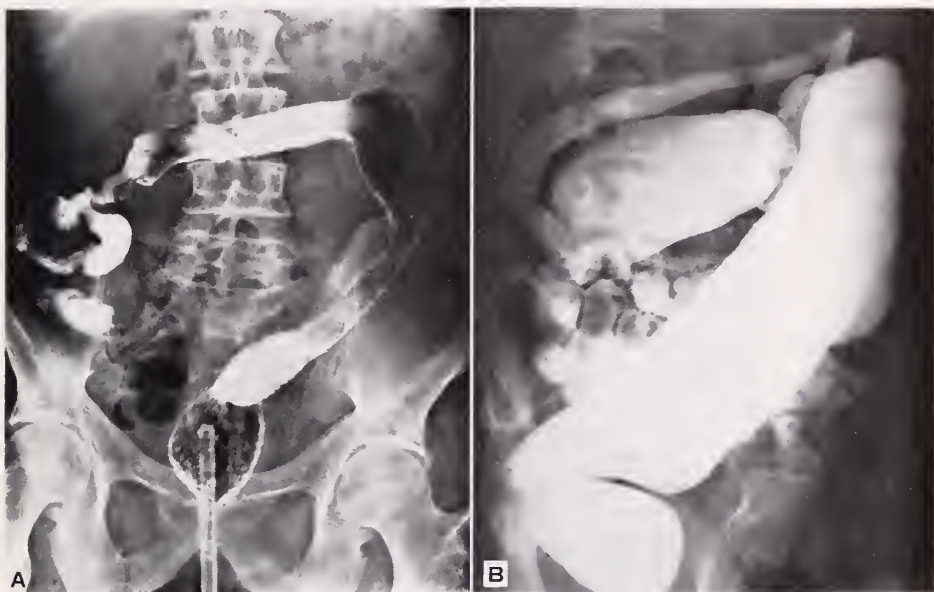


Fig. 16A. Universal chronic ulcerative colitis. There is a marked degree of narrowing, rigidity and shortening. The mucosal pattern is absent with a few inflammatory polyps. Shortening of right side of colon is marked and the anatomical landmarks are difficult to identify. Terminal ileum is elevated.

Fig. 16B. Unusual case of segmental ulcerative colitis, chronic phase involving right side of colon. Right side of colon has tubular, pipe-stem appearance with enormous dilatation of terminal ileum. The tubular, rigid, symmetrical appearance is in contrast to the asymmetrical appearance of granulomatous colitis. The inflammatory process confined to right side is unusual for ulcerative colitis. A similar appearance is seen in ischaemic infarction of the colon.

barium enema examination is contraindicated. Nevertheless, this examination has been attempted in several instances without apparent complications, probably because it is impossible to introduce large quantities of barium without inducing evacuation. The examiner also finds it useless to continue the examination because of the large amount of secretions and air within the colon. However, the barium may outline some of the features (Fig. 22, 23), which consist of distention, obliteration of the haustral and mucosal pattern, irregularity of the contour with multiple deep projections indicative of ulceration and numerous nodular pseudopolypoid intraluminal projections. There may be shortening

and lack of redundancy of the colon and an inability of the colon to contract because of loss of tone.

### *Benign Strictures and Carcinoma*

According to the formal criteria of stricture, benign strictures in ulcerative colitis are uncommon (2). The term stricture is applied to a localized, rigid, filiform narrowing which has produced some antegrade obstruction. On roent-



FIG. 17. Universal ulcerative colitis, chronic phase. This appearance of narrowing, rigidity, absent mucosal markings, with little shortening has been referred to as chronic burnt-out ulcerative colitis.

gen examination, the strictures have a typically benign appearance with a concentric lumen, smooth contours and fusiform, pliable tapering margins (Fig 24). The bowel proximal to the stricture is minimally dilated and on evacuation the colon empties well. Occasionally, however, the lumen of the stricture is slightly eccentric with irregularity of the contours and mucosa simulating a carcinoma (Fig 25). Rarely a small sinus tract is demonstrated, extending laterally from the distal portion of the stricture. Despite the roentgen findings of chronic ulcerative colitis, microscopic examination frequently reveals active inflammation at the site of the stricture and immediately proximal and distal to it. The genesis of these strictures is unknown but may be due to a localized

perforation in a markedly inflamed bowel. If operative removal of the stricture alone is performed, postoperative follow-up is of interest. In some patients fistulas form at the site of anastomosis and ultimately heal. In others the remainder of the colon becomes the seat of a fulminating ulcerative colitis necessitating a colectomy and ileostomy. It would appear that if a diagnosis of benign stricture can definitely be made, conservative treatment is indicated as segmen-



FIG. 18. Toxic dilatation of colon in ulcerative colitis. There is moderate distention of the transverse colon. Tooth-like serrations probably due to deep ulcerations are seen along superior border of proximal transverse colon.

tal resection on a colon previously involved with inflammatory disease is frequently followed by complications.

An interesting situation occurs when the right side of the colon is shortened with stricturing of the ileocecal valve and colonization and dilatation of the terminal ileum. The anatomical landmarks are so distorted that the irregular, stenotic ileocecal region suggests a carcinoma in the colon. The dilated terminal ileum could easily be mistaken as a segment of colon and a narrowed ileocecal valve for a carcinoma (Fig 26 A and B).

Carcinoma of the colon developed in six per cent of our ulcerative colitis patients. In two-thirds of these the colitis was chronic and burnt-out. In one third the colitis was active, with evidence of ulceration and inflammatory polyps. In



some cases the carcinoma presents as a filiform stricture with none of the typical roentgen alterations associated with a carcinoma. The roentgen findings in these cases include a narrowed segment, usually measuring 2 to 6 cm in length with an eccentric lumen, irregular contours and flattened, rigid, tapered margins (Fig 27A, B, 28, 29A, B, 30). There is a moderate degree of dilatation of the proximal bowel with evidence of increased secretions and retained stool. Clinically, symptoms of colonic obstruction are a prominent feature. The dis-



FIG. 19. Toxic dilatation in ulcerative colitis. Marked distention of transverse colon and midportion of descending colon. The haustral markings in these regions are absent, with numerous polypoid projections due to large inflammatory polyps. Considerable irregularity of contour of the bowel.

tal transverse colon, descending colon and the rectum are the most frequent sites of carcinomatous strictures in our series of cases. The atypical roentgen features are probably due to the associated inflammatory disease and the submucosal location of the carcinomas. Pathological study shows the deep layers of fibrous tissue infiltrated by scirrhous carcinoma. An irregular stricture in the presence of chronic ulcerative colitis should be considered as a carcinoma until proven otherwise.

In the remaining cases, the carcinoma, in spite of the underlying ulcerative



colitis demonstrated the typical roentgen alterations associated with a malignancy and presented no problem in differential diagnosis (Fig 31).

### *Backwash Ileitis*

Statistics quoting involvement of the ileum in patients with ulcerative colitis vary from 5 to 30 per cent. In our series it occurred in approximately ten per cent. The involvement of the mucosa is minimal and the length of involvement variable (4 to 20 cm). There is no significant narrowing of the bowel lumen. The contours are smooth or slightly serrated. The amount of secretions and

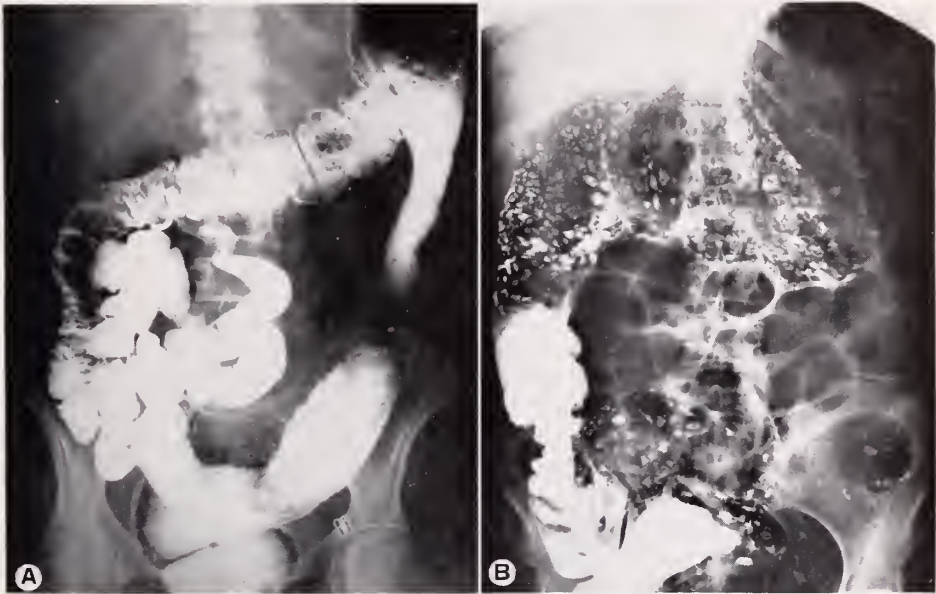


Fig. 20A. Chronic ulcerative colitis. Barium enema examination shows the moderately severe changes of ulcerative colitis from splenic flexure to rectum. Sigmoid is moderately dilated. Right side of colon is minimally involved.

Fig. 20B. Same case as Fig. 20A; toxic dilatation of colon. At this time there is huge distention of transverse colon. Distention of the sigmoid has increased but the caliber of the descending colon is unchanged. Appearance of the barium in transverse colon suggests marked ulceration and numerous inflammatory polyps.

motor activity are minimally increased (Fig 32A). The findings in the ileum are limited in degree and extent even when the roentgen alterations in the colon are marked.

In an occasional case of "backwash ileitis" the distinction from regional enteritis may be difficult. More extensive ulceration of the mucosa may produce spasm with narrowing and rigidity and in these cases differential diagnosis may be impossible (Fig 32B).

### *Reversibility in Ulcerative Colitis*

Not infrequently as serial examinations are performed in patients with ulcerative colitis there appears to be considerable healing of the inflammatory

process with a marked reversibility in the appearance of the colon (Fig. 33A and B). The narrowing of the lumen has been reported to disappear, the haustral pattern to return to normal and the inflammatory polyps to vanish. In analyzing these cases, however, it becomes apparent that not all of them demonstrate true reversibility. The narrowing may have been due to an acute stage when there is considerable associated spasm and irritability. Actual fibrotic narrowing may never have been present. The reappearance of a normal haus-



FIG. 21. Mild toxic dilatation of colon. Slight dilatation of transverse colon with considerable irregularity of the contours indicating severe ulceration.

tral pattern may also be misleading because the haustra, especially when irregular and thick, can represent pseudohaustrations produced by underlying severe inflammatory disease. Nevertheless, reversibility to some degree is an established feature of ulcerative colitis.

On the other hand, it should be noted that at any time in the course of ulcerative colitis an acute flare-up may occur and there may be a marked change in the roentgen appearance of the inflamed bowel. This is most dramatically seen in patients with minimal involvement when subtle roentgen alterations become florid with rapid development of severe ulcerations and pseudopolyps.

*Differential Diagnosis**Familial Polyposis*

The colon in a patient with ulcerative colitis may contain a tremendous number of pseudopolyps. As a result, the appearance may sometimes be confused with familial polyposis (3). In a majority of cases of ulcerative colitis associated with pseudopolyps there is some roentgen evidence of an inflammatory



FIG. 22. Barium enema examination in patient with mild toxic dilatation. Diffuse involvement of colon with numerous inflammatory polyps. The dilatation in this case is confined to right side of colon and is of moderate severity.

process manifested by absence or irregularity of the haustral margins, narrowing of the lumen, longitudinal shortening of the colon and ulceration of the mucosa (Fig 34 A and B). On the contrary, in the cases of familial polyposis that we have studied there is usually no evidence of an inflammatory process on roentgen examination despite the presence on pathological examination of minimal inflammatory changes in many of these cases. It should be noted that differentiation between the two entities from the appearance of the polyps themselves is unreliable (Fig 35A and B). A perplexing situation can develop in an occasional case of ulcerative colitis in which the inflammatory process heals

and the roentgen changes return to normal but a large number of inflammatory polyps remain (Fig. 35, 37A-D). In these cases involvement of the ileum with backwash ileitis may aid in differentiation. Familial polyposis rarely involves the small bowel.

### *Cathartic Colon*

The roentgen findings of cathartic colon may be difficult to differentiate from burnt-out ulcerative colitis (4) (Fig 38, 39). In cathartic colon the right side



FIG. 23. Attempted barium enema examination in patient with toxic dilatation. The considerable secretions obscure the details observed in toxic dilatation. Barium enema examination in these cases is frequently futile and is unnecessary for diagnosis.

reveals the more extensive alterations. These consist of absent or diminished haustral markings, bizarre contractions and inconstant areas of narrowing. The bowel is moderately distensible, and after evacuation barium is frequently retained within the colon. The mucosal pattern, when identified, is usually linear or absent with no evidence of ulceration. In severe cases the left side of the colon may also be involved, but the sigmoid and rectum are usually normally distensible. The terminal ileum can manifest changes similar to the right side of the colon for varying lengths. The ileocecal valve is frequently flattened and gaping. Shortening of the colon occurs, especially on the right side, but the



flexures are usually normally situated. Fluoroscopically and on the films, tubular areas of narrowing may be identified. These reveal a concentric lumen with tapering margins and no evidence of rigidity. The areas of narrowing are inconstant and may disappear during a single examination.



FIG. 24. Chronic burnt-out ulcerative colitis with benign stricture. There is a fusiform tapering stricture with a concentric lumen and smooth contours measuring 1.5 cm in length in the mid-descending colon. There is moderate degree of dilatation proximal to the stricture, with retained stool and secretions. Entire colon is involved with chronic burnt-out ulcerative colitis.

#### GRANULOMATOUS COLITIS

Patients with granulomatous colitis, like those with ulcerative colitis, may present with fever, abdominal cramps and diarrhea or constipation (5, 6). Gross blood in the stools, however, is unusual and when it does occur it tends to be infrequent and not a prominent feature of the illness. Perianal fistulae and anorectal disease are common in granulomatous colitis and, as has been observed in regional enteritis, they may appear before any of the other clinical features of the disease. Extracolonic manifestations are less common than in ulcerative colitis. Although the rectum may be involved in granulomatous disease, the process tends to be right sided, segmental and to spare the rectum.



Thus a normal sigmoidoscopy in a patient with colitis is strongly suggestive of granulomatous disease. Clinical distinction in the appearance of an involved rectum between ulcerative and granulomatous disease may be difficult, but an irregularly inflamed, cobblestone surface, if present, suggests the latter (7). Rectal biopsy reaching the submucosa may yield granulomas. Carcinoma of



FIG. 25. Benign stricture in chronic ulcerative colitis. There is a slightly irregular stricture measuring 3.5 cm in length in the proximal descending colon. A sinus tract extends laterally from distal portion of stricture. There is minimal proximal dilatation. It is impossible in this case to make a definite diagnosis of benign or malignant stricture. Pathologic examination revealed a benign stricture.

the colon thus far has not been reported in association with granulomatous colitis. Free perforation of the colon into the peritoneal cavity is rare even though minute, sealed-off perforations are characteristic of the granulomatous disease process.

The medical treatment of granulomatous colitis is similar to that of ulcerative disease and is largely symptomatic and supportive. Corticosteroids are useful in management but are less likely to induce a full remission than in ulcer-



FIG. 26A. Benign stricture in chronic ulcerative colitis. Right side of colon is markedly shortened with complete disappearance of normal cecum and ascending colon. There is stricturing and irregularity of ileocecal valve with dilatation of terminal ileum. Failure to recognize the dilated terminal ileum may result in a mistaken diagnosis of a carcinoma. *Operative findings:* Ulcerative colitis with benign stricture of ileocecal valve.

FIG. 26B. Same case as Fig. 26A, spot film of benign stricture.

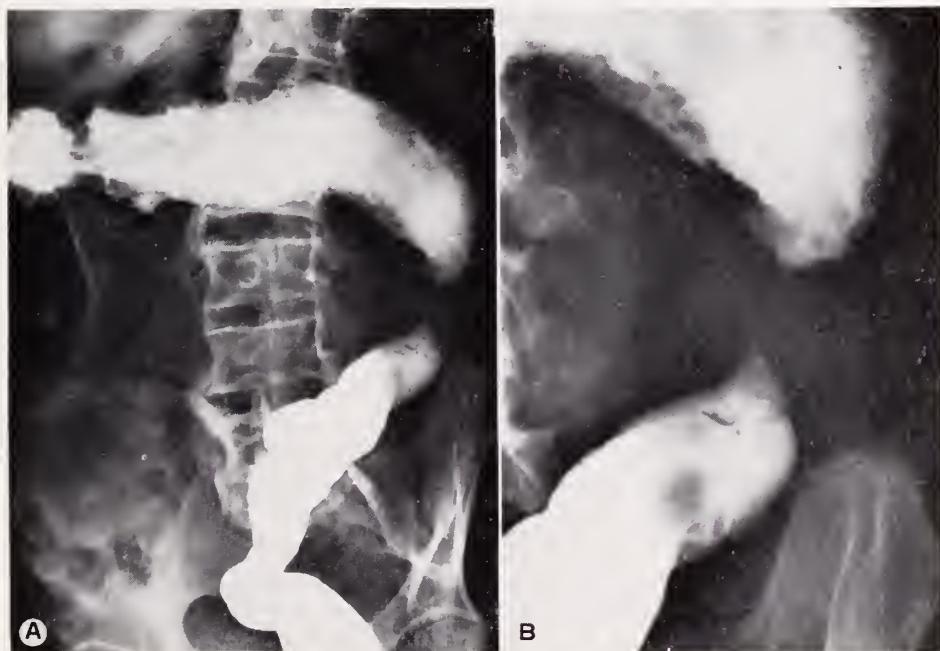


FIG. 27A and B. Carcinomatous stricture in chronic ulcerative colitis. The stricture involves the proximal descending colon. The lumen is eccentric, the contours irregular and there is moderate dilatation of proximal bowel. An irregular stricture in ulcerative colitis must be considered a carcinoma until proven otherwise.

ative colitis. In some patients with granulomatous colitis the disease runs a relatively low grade and indolent course with moderate disability. When surgery is required in these patients it is usually for obstruction. In other patients the course of the disease is more severe; fistula formation and sinus tracts are common and infection and chronic toxicity become indications for surgery.

The problem of surgical treatment is more complicated in granulomatous than in ulcerative disease. In ulcerative colitis the disease is curable at the ex-



FIG. 28. Carcinoma of rectum with ulcerative colitis. Irregular marked narrowing of entire rectum due to carcinoma in patient with chronic burnt-out ulcerative colitis. Numerous nodular defects are also identified in the strictured area.

pense of total colectomy and ileostomy. In granulomatous disease of the small intestine (regional enteritis) lengths of bowel which appear normal at operation may become involved in granulomatous disease after resection or bypass procedures. Such recurrence develops in at least half the patients. Similar recurrence has also been noted in patients with granulomatous disease of both ileum and colon (ileocolitis). It appears at present, for reasons not yet clear, that when surgery is performed in patients with granulomatous colitis in whom the small bowel is normal, the recurrence rate is considerably less. Nevertheless, since the pathology of small bowel and colonic granulomatous disease is the

same, the risk of postoperative spread of disease must be kept in mind. For this reason, patients with granulomatous colitis, like those with regional enteritis, are managed medically as long as possible and surgery reserved for complications or for prolonged disability.

The lesions characteristic of regional enteritis may be seen in any segment of the colon with or without associated disease in the small intestine. The colon may be involved in granulomatous disease in one of several ways. In the first place, the colon alone may be the site of primary granulomatous disease, sometimes in its entirety, but more frequently in segmental fashion, the rectum and

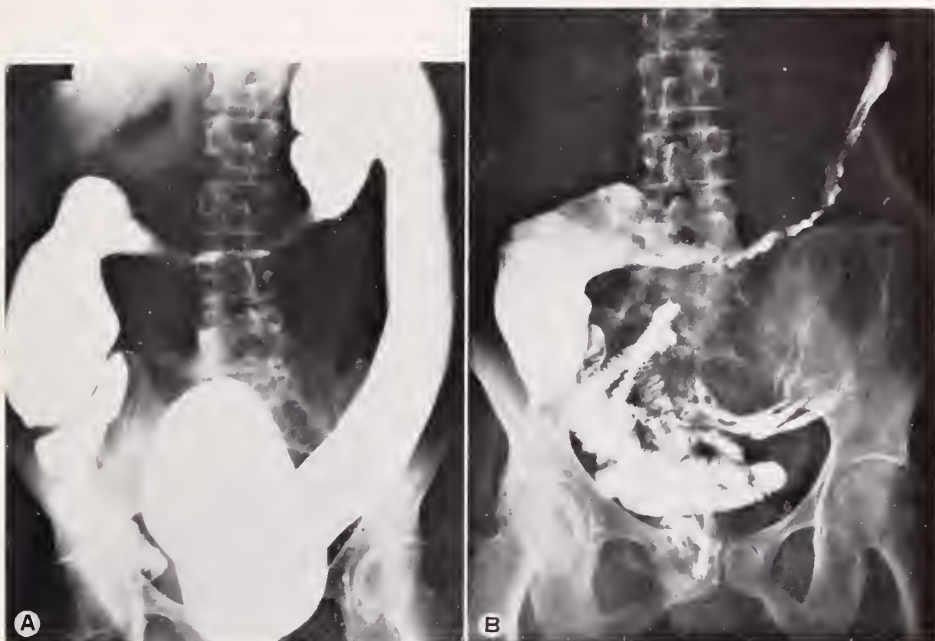


FIG. 29A. Long carcinomatous stricture in chronic burnt-out ulcerative colitis.  
FIG. 29B. Same case as Fig. 29A, evacuation film.

sigmoid being spared. Second, in addition to granulomatous disease of the colon there may be involvement, usually simultaneous in onset, of the small bowel. The diseased area in the colon may be continuous with that in the ileum or it may present as a skip lesion with normal intervening bowel. Third, the colon may become involved with granulomatous disease only after an operation has been performed for regional ileitis. Here the diseased segment of colon is usually immediately adjacent to an anastomosis. Finally, the colon may be involved directly by fistula formation from a loop of bowel that is the site of regional ileitis. Such fistulas, in our experience, are usually without significance so far as subsequent development of granulomatous colitis is concerned; the disease does not appear to spread and the area heals when the diseased small bowel has been removed and the fistula closed.





FIG. 30. Carcinomatous stricture in chronic ulcerative colitis. Irregular stricture involving the proximal descending colon with an eccentric lumen and marked dilatation of proximal bowel. Entire colon is involved with burnt-out ulcerative colitis.

Thus the colon itself can be involved in a primary granulomatous process or both colon and small bowel, usually ileum, can be the site of granulomatous disease. Such associated involvement we have termed granulomatous ileocolitis. The term ileocolitis is used only to describe granulomatous disease and does



not refer to ulcerative colitis with backwash ileitis. As has been noted, the ileal involvement in ulcerative colitis does not alter the course of the colonic disease or its management and is thus of little clinical significance. We believe that regional ileitis and ulcerative colitis are associated only rarely and by chance. Pending full understanding of the etiologic agents involved, it seems reasonable that when regional ileitis is present the associated inflammatory dis-



FIG. 31. Carcinoma in chronic burnt-out ulcerative colitis. The classical appearance of a carcinoma is noted in the proximal descending colon.

ease in the colon should be granulomatous and this has been the case in recent studies.

Not every segmental colitis, however, is granulomatous. Ulcerative colitis can at times present in segmental, right-sided or atypical forms and may be associated with minimal inflammatory changes in the terminal ileum. These lesions must be differentiated from granulomatous colitis and ileitis.

The pathology of granulomatous colitis is similar to that of regional enteritis (8, 9). There is a chronic inflammation extending through the entire wall involving primarily the submucosa. The bowel wall is thick and rigid with narrowing of the lumen which may lead to stricture formation. Ulcers are deep and tend to present as long linear ulcerations intersecting with deep transverse

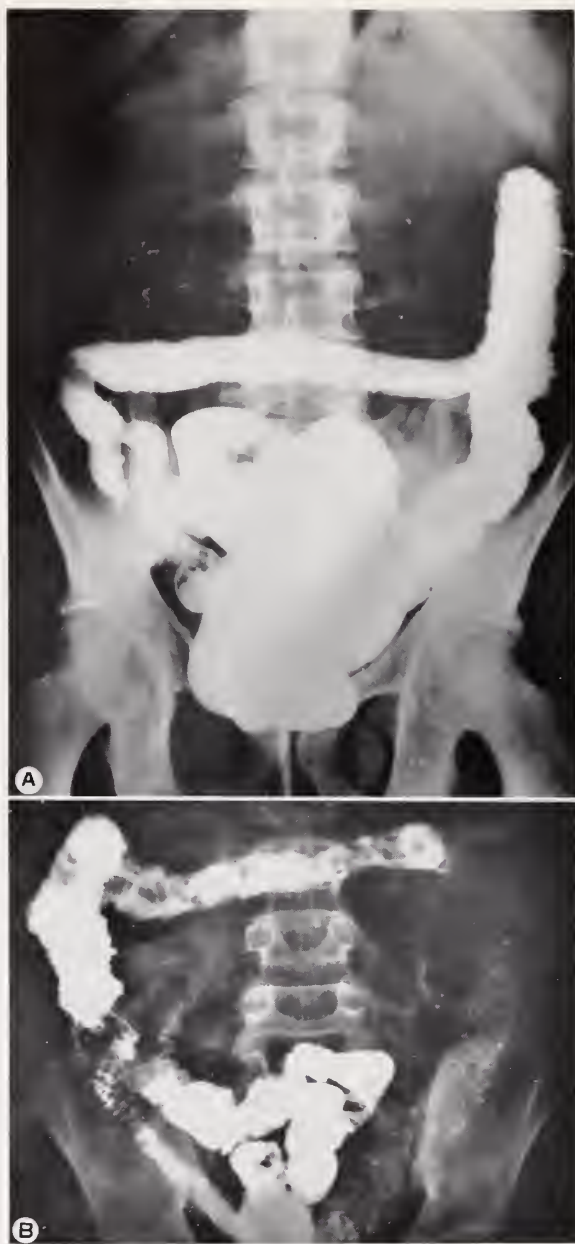


FIG. 32A. Ulcerative colitis with backwash ileitis. Terminal ileum is distensible associated with minimal irregularity of the contour and increased secretions. The narrowing and rigidity usually associated with regional enteritis is absent. Inflammatory process involving the colon is evident.

FIG. 32B. Diffuse ulcerative colitis with backwash ileitis. The backwash ileitis in this case is unusually extensive and mimics regional enteritis. There is moderate degree of narrowing and rigidity with slight irregularity of the contour and thickening of the mucosal folds. The more marked involvement of the ileum in this case suggests granulomatous disease. At operation, however, the findings were those of ulcerative colitis and backwash ileitis.

ulcers or fissures. The intervening mucosa is swollen and the luminal surface has a coarsely nodular appearance which has been likened to a cobblestone road. Involvement of the bowel wall itself may be asymmetrical rather than circumferential. Loops of involved gut may be adherent to each other or to loops of normal bowel. Fistulae between loops of bowel or to other viscera are common and intra-abdominal abscesses may be present. When the ileum as well as the colon is involved in this inflammatory process the condition is called granulomatous ileocolitis (Fig 40-44).

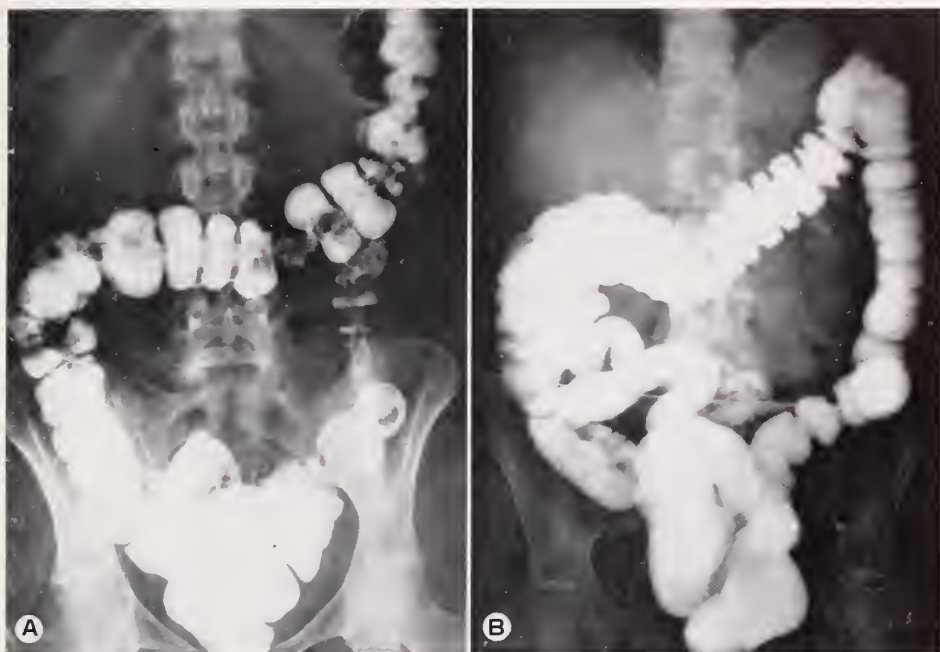


FIG. 33A. Reversibility in ulcerative colitis. Same case as Fig. 1 and 2, six months later. Remarkable reversibility in appearance of the colon. There is no roentgen evidence of an inflammatory process. The haustral markings are within normal limits. A moderate amount of stool is present in colon due to incomplete preparation.

FIG. 33B. Reversibility in ulcerative colitis. Same case as Fig. 10 and 11, one year later. The ileum and colon now appear normal. Reversibility is a feature that is more commonly identified in ulcerative than in granulomatous colitis.

Histological examination shows a chronic inflammatory reaction most prominent in the submucosa but extending through the bowel wall with edema and fibrosis. The ulcers are deep and extend through the serosa as sealed-off perforations to which adjacent viscera may adhere. The characteristic histological feature is the presence of noncaseating granulomas with Langhans' giant cells and epithelioid cells. Especially when ulceration is severe, granulomas may be scanty or absent, but a diagnosis of granulomatous disease is warranted if the other characteristic pathological features are present. Regional lymph nodes may be enlarged and on section show characteristic granulomas.

Roentgenographic features characteristic of granulomatous colitis are essen-



FIG. 34A. Ulcerative colitis with inflammatory polyps simulating familial polyposis. Numerous inflammatory polyps distributed throughout the colon. The narrowing, rigidity and shortening are evidence of an inflammatory process and differentiate the findings from familial polyposis. Differential diagnosis on the basis of the appearance of the polyps alone is impossible.

FIG. 34B. Ulcerative colitis with inflammatory polyps simulating familial polyposis. In this case it is even more difficult to differentiate the findings from familial polyposis. There is, however, slight narrowing and lack of distensibility of transverse and descending colon. Note lack of involvement of rectum.





tially those seen in regional enteritis of the small bowel (10). They include skip lesions, longitudinal ulcerations, transverse fissures, deep ragged ulcerations, eccentric involvement and pseudodiverticula, narrowing or stricture for-



FIG. 36. Ulcerative colitis simulating familial polyposis. There is so little evidence of an inflammatory process in this case that differential diagnosis from familial polyposis would be impossible in the absence of previous films which demonstrated the characteristic changes of ulcerative colitis. The filling defects were constant and due to polyps rather than stool.

mation, pseudopolypoid changes producing a coarse cobblestone pattern, internal fistulae and sinus tracts (Fig 45-60).

In early or minimally involved cases many of the typical roentgen features of granulomatous disease may not be seen. Instead, there are single or multiple nodular defects or irregularity and rigidity of the contour of a short seg-

FIG. 35A. Typical appearance of familial polyposis involving the entire colon. The polyps are more readily distinguishable on the left side. The bowel is more distensible than is usually noted. There is no evidence of an inflammatory process.

FIG. 35B. Same case as Fig. 35A, air study. The tremendous numbers of polyps are again identified. Individual pedicles are difficult to delineate.



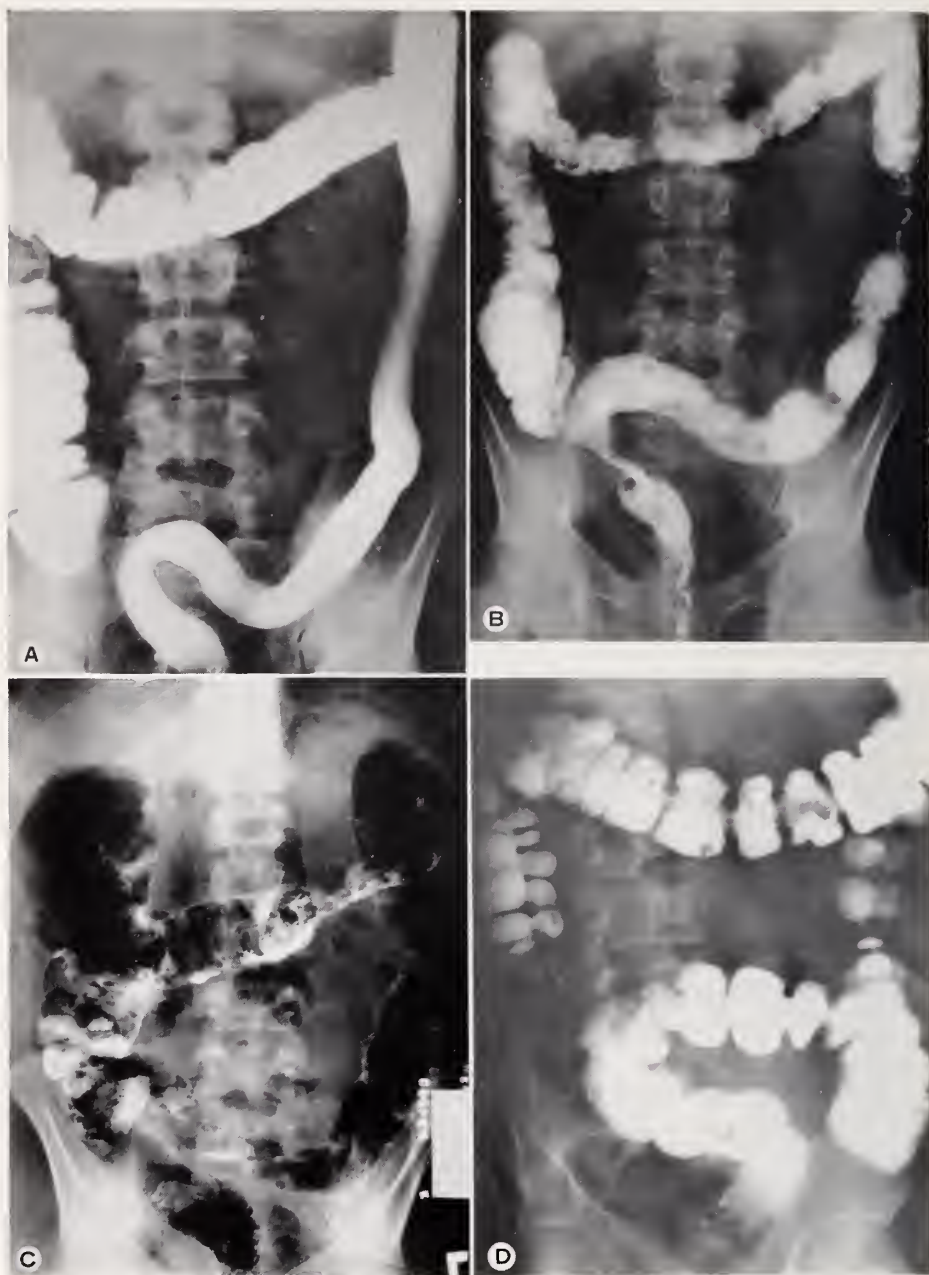


FIG. 37A. Ulcerative colitis involving predominantly the transverse colon, descending colon and rectum.

FIG. 37B. Same case one year later. There is more marked involvement of the colon. Numerous large inflammatory polyps can be identified.

FIG. 37C. Same case three years later. Air study again reveals the large inflammatory polyps. There is narrowing in the distal transverse colon, sigmoid and rectum. Remainder of the bowel is more distensible than on previous examination.

ment (Fig 61). These minimal changes can easily be obscured by filling and distention of the colon or by overlapping adjacent bowel. The mucosal pattern after evacuation is helpful in these cases as it may reveal thickening or nodularity of the mucosa with an irregular rope-like appearance (Fig 62 A, B, and C, 63). Although small areas of ulceration may be difficult to identify, their presence may be suggested by straightening or rigidity of a segment or by the presence of pseudodiverticula on the opposite wall. This is due to the fact that ulceration produces spasm and contraction and the opposite uninvolved wall becomes folded. The small ulcers combine to produce large longitudinal

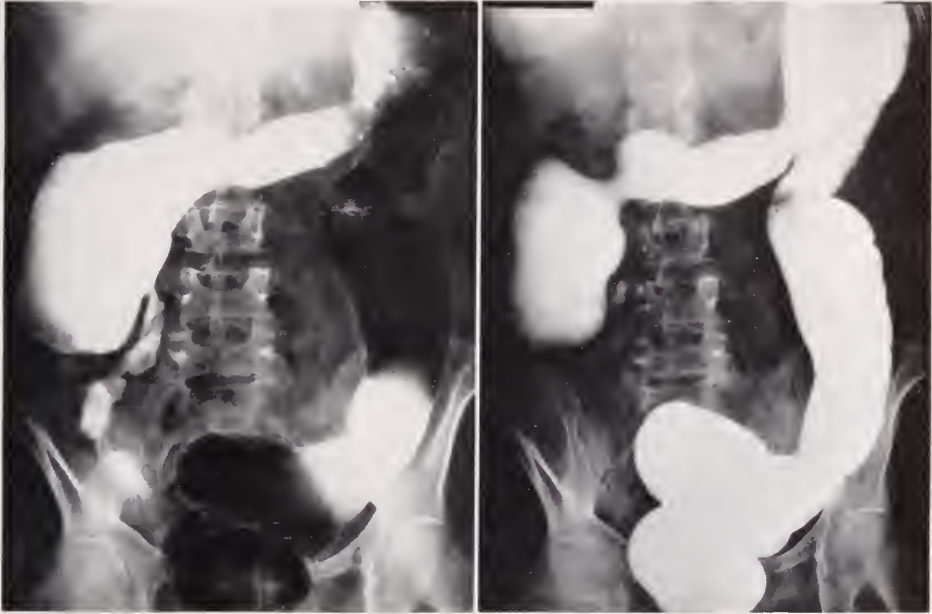


FIG. 38. Cathartic colon. Normal distensibility with complete absence of the haustral markings. The findings are more obvious on right side of colon. Areas of narrowing are inconstant.

FIG. 39. Cathartic colon simulating burnt-out ulcerative colitis.

ulcerations or gutters which are frequently multiple. When this is associated with transverse linear ulcerations it produces the characteristic cobblestone pattern (Fig 64).

The transverse ulcers may penetrate beyond the contour of the bowel so as to present in profile as numerous long, thin spicules, perpendicular to the long axis of the bowel or as a sinus tract (Fig 65 A, B, and C). They are most frequent between terminal ileum and cecum (Fig 66) and may ultimately lead

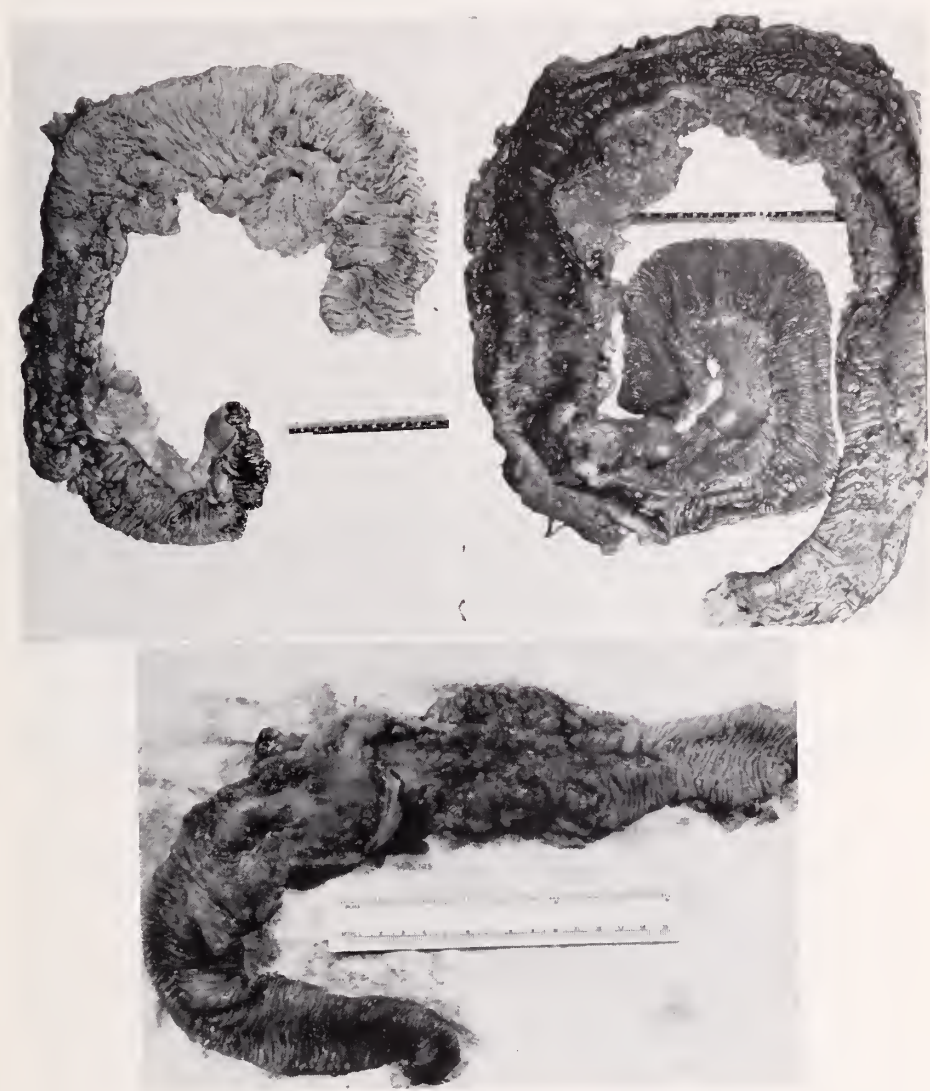
FIG. 37D. Same case six years after initial examination. There is now a carcinomatous stricture of the rectum and a carcinoma of the sigmoid. Remainder of colon reveals a remarkable reversibility in the appearance of the inflammatory process; after colectomy and microscopic study the pathologist had difficulty in determining whether the findings were due to familial polyposis or ulcerative colitis. The serial roentgen films demonstrating the presence of ulcerative colitis were helpful in arriving at the final diagnosis of chronic ulcerative colitis with two superimposed carcinomas.

Fig. 40-44: Characteristic Pathologic Features of Granulomatous Colitis





to intramural abscesses (Fig 67). These abscesses at times are large, producing a marked irregularity of the contour of the bowel. When they penetrate into the adjacent loops, a fistula is formed (Fig 65C). Intestinal fistulae are less fre-



FIGS. 42-44

Cobblestoning, longitudinal ulcerations, skip lesions, stricturing and thickening of bowel wall are seen. In Fig. 44 the pathologic features in terminal ileum and right side of colon are similar.

quent in granulomatous disease of the colon, however, than in regional enteritis. In late stages of the disease, the entire mucosa may be sloughed off because of the diffuse ulceration. In those cases in which the bowel is diffusely and symmetrically involved and there are no typical features of granulomatous disease



FIG. 45. Granulomatous colitis. Marked irregularity of the contours due to numerous large sac-like ulcerations. Left side of colon is normal.

FIG. 46. Granulomatous colitis. Narrowing and irregularity of the transverse and proximal descending colon. Pseudodiverticula and pleating of the folds are seen along medial



differentiation from ulcerative colitis may be impossible, especially in the absence of characteristic features in the small intestine (Fig 68, 69, 70).

Since marked thickening of the bowel secondary to intramural fibrotic changes is common in granulomatous colitis, irregular stenotic segments and strictures are frequently seen (Fig 71-75). Occasionally granulomatous colitis presents as a single stricture of the colon (Fig 76). When this stricture is eccentric and associated with overhanging edges, differentiation from a carcinoma

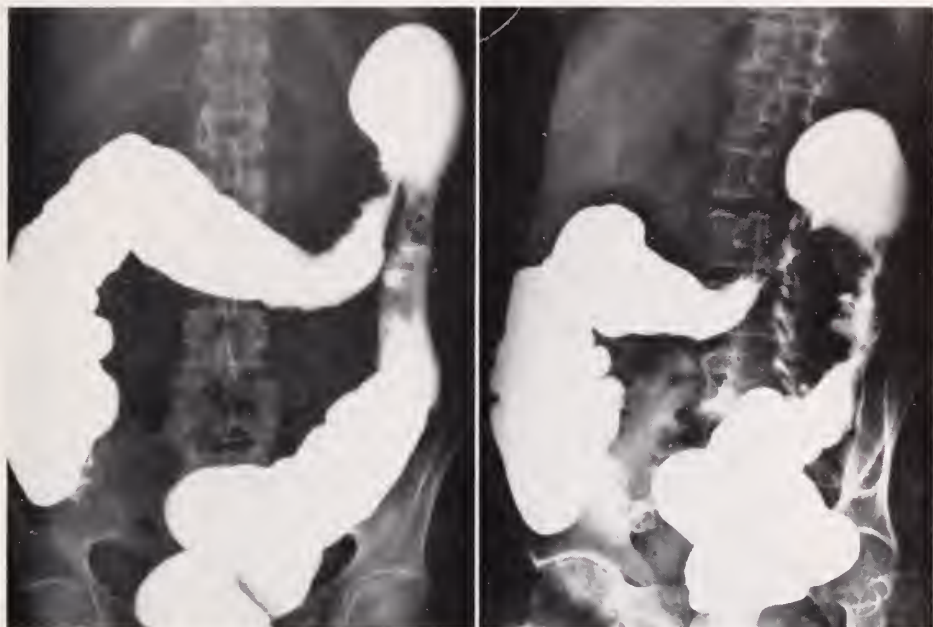


FIG. 48. Granulomatous colitis. There are two skip lesions; one in distal transverse colon and the second in proximal descending colon with normal intervening bowel. There is marked irregularity of the contour and large inflammatory polyps.

FIG. 49. Same case as Fig. 48. One year later the skip lesions are again identified. At this time pseudodiverticula are seen in descending colon reflecting asymmetrical involvement.

may be impossible. In most cases, however, there is further evidence of involvement of the bowel in the form of skip lesions, further strictures, or other identifying features of granulomatous disease.

Granulomatous colitis can also resemble burnt-out ulcerative colitis, except for its more frequent segmental distribution, usually right-sided. There is minimal narrowing or rigidity associated with absent haustral markings and effacement of the mucosa. These cases probably represent minimal degrees of involve-

aspect of proximal descending colon. This case represents a later stage of involvement than the case shown in Fig. 45.

FIG. 47. Granulomatous colitis. More marked narrowing and irregularity of the transverse colon and proximal descending colon with considerable dilatation of right side of colon. Characteristic segmental distribution is identified.

ment with little scarring (Fig 77). They are present at a time when none of the typical roentgen features of granulomatous colitis is present.

Linear extension of the disease in granulomatous colitis, as in regional enteritis, is uncommon in the absence of surgery, but normal areas between skip lesions may become involved. A minimally involved colon with multiple skip lesions may become severely and diffusely ulcerated in a short period of time.

Granulomatous colitis must be differentiated not only from ulcerative colitis



FIG. 50. Granulomatous colitis. Spot film of right side of colon demonstrating transverse and linear ulceration. Large inflammatory polyps, narrowing, rigidity and irregular contours.

but also from several other conditions of the colon. This may be difficult when the area involved is single and limited in extent. In such instances diverticulitis, carcinoma, foreign body perforations, or infarction may be simulated. In diverticulitis the mucosa is intact, diverticula are present, and a localized extrinsic mass due to abscess formation may be evident. In carcinoma a rigid mass with elevated or overhanging edges is characteristic. Complete obstruction is rare in granulomatous disease despite the fact that short segments may become markedly narrowed. In infarction the early stage may mimic granulomatous colitis. There is marked thickening of the folds, spasm, irritability and increased secretions. Follow-up studies frequently reveal the rapid devel-

opment of a stricture. In other instances the bowel returns to normal. In the absence of follow-up studies, differential diagnosis may be impossible.

Since ileostomy and colectomy are performed for both ulcerative and granulomatous colitis, the development of inflammatory disease in the ileum proximal to the stoma is pertinent. Such prestomal ileitis may be of two varieties. One is secondary to obstruction of the stoma (ileostomy dysfunction) and is a



FIG. 51. Granulomatous colitis; spot film of rectum and sigmoid. Submucosal nodules, associated with irregularity of the contour, narrowing and rigidity. The submucosal nodules probably represent tiny ulcerations with surrounding edema. The thickening of the submucosa also plays a role in genesis of these nodules.

mechanical problem related to narrowing of the stoma. The other is secondary to extension of the granulomatous process. Ileostomy dysfunction may be seen in both ulcerative colitis and granulomatous colitis. Extension of the granulomatous process is only seen if operation is performed for granulomatous disease. It is of considerable interest that in our series of cases, prestomal granulomatous ileitis has been noted only in patients in whom the involvement was in both small bowel and colon. It has not been identified in those patients in whom the granulomatous process has been confined to the colon alone, although this has been reported by others.



FIG. 52. Granulomatous colitis. There is a fistulous communication between a narrowed transverse colon and the duodenum. Fistulae are a feature of granulomatous colitis rather than ulcerative colitis.



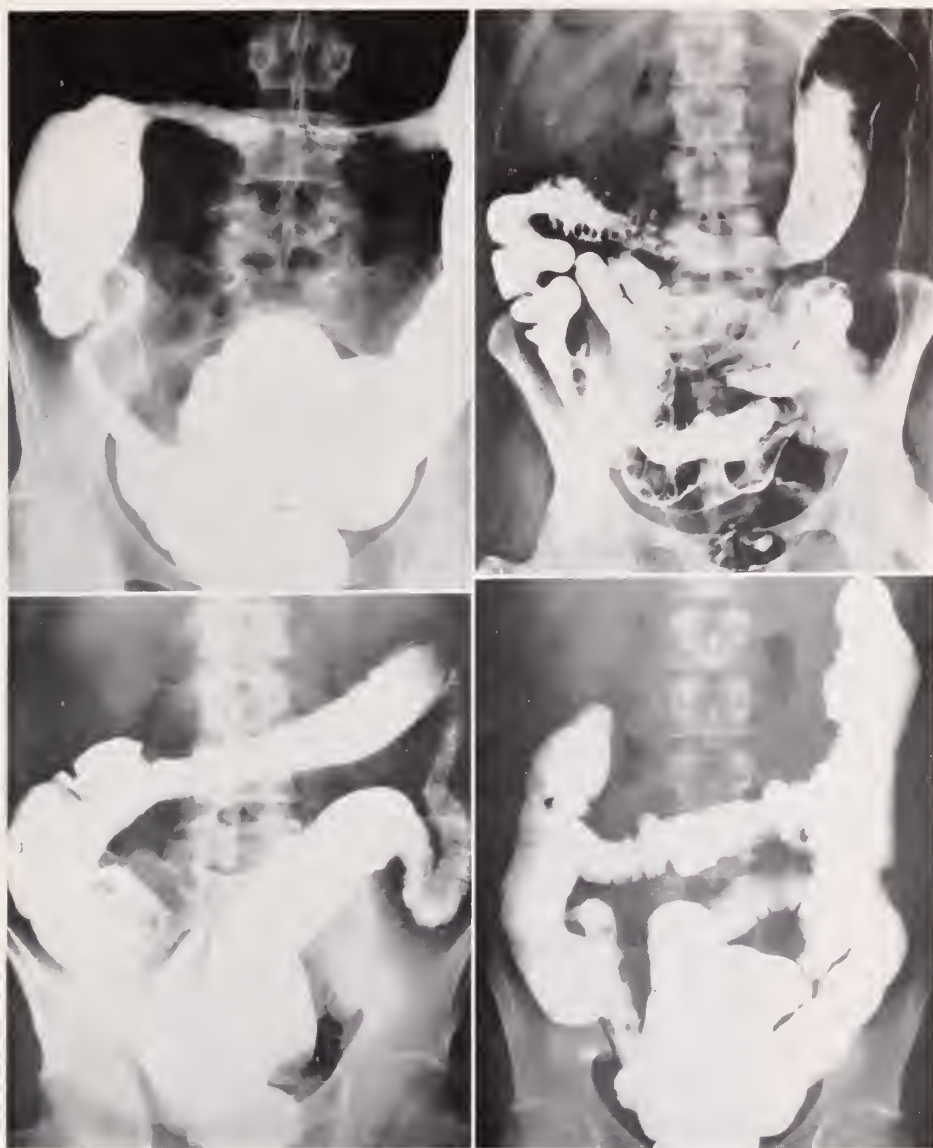


FIG. 53. Granulomatous ileocolitis. Simultaneous and similar involvement of the ileum and right side of the colon characterized by narrowing and rigidity of the ileum and transverse colon. The ascending colon is fairly distensible. Left side of colon is normal.

FIG. 54. Granulomatous ileocolitis. Ileum and right side of the colon are involved. Transverse ulcerations and inflammatory polyps are seen in right side of transverse colon. A small fistulous communication from the ileum to the cecum is noted. Left side of colon is normal.

FIG. 55. Granulomatous ileocolitis. The findings are severe in the descending colon where there is narrowing, rigidity and marked ulceration. The inflammatory process is segmental. The unevenness of involvement is another characteristic feature of granulomatous disease.

FIG. 56. Granulomatous ileocolitis. The ileum and the colon to the splenic flexure are involved with typical regional enteritis. A small skip lesion is identified on the lateral aspect of mid-descending colon.



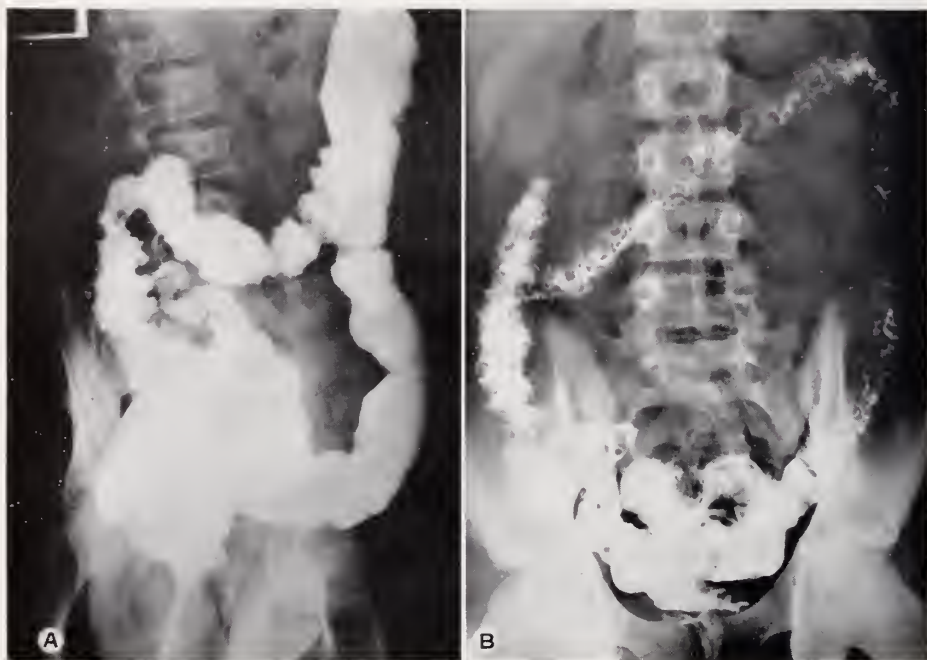


FIG. 57A. Granulomatous ileocolitis. Narrowing and rigidity of the terminal ileum and colon. Gross irregularity of the contour is seen. There is minimal involvement of the descending colon. Rectum and sigmoid are normal.

FIG. 57B. Same case as Fig. 57A, evacuation film. The mucosa is thickened, hazy and irregular with numerous small nodules. The nodular appearance is in contrast to the thickened symmetrical mucosal folds seen in ulcerative colitis. Extent of involvement in this case is better determined on the evacuation film.



FIG. 58A. Regional enteritis with extension into the colon. The terminal ileum is involved with the characteristic findings of regional enteritis. Colon appears normal.

FIG. 58B. One year later, evacuation film. Marked involvement of the entire colon with a sinus tract extending lateral to the descending colon. The mucosa has a cobblestone appearance with numerous and longitudinal ulcerations. In granulomatous disease extension in the absence of surgery is uncommon.



FIG. 59. Granulomatous ileocolitis. Inflammatory process involves primarily the right side of colon. There is a skip lesion in the terminal ileum. In the absence of the characteristic findings of regional enteritis, a definite diagnosis of granulomatous disease in the colon would be difficult.



FIG. 60. Granulomatous ileocolitis. Roentgen findings in the ileum are due to regional enteritis. In colon the findings are minimal and characterized by slight flattening of the contours and minimal distortion of the haustral markings. The findings in terminal ileum indicate that the subtle findings in the colon are due to granulomatous colitis.



FIG. 61. Granulomatous colitis involving transverse colon. There is minimal involvement of the inferior aspect of the transverse colon characterized by irregularity and nodular filling defects. The findings are partially obscured by over-filling of colon with air. These minimal findings are frequently better identified on a motility film or evacuation film.



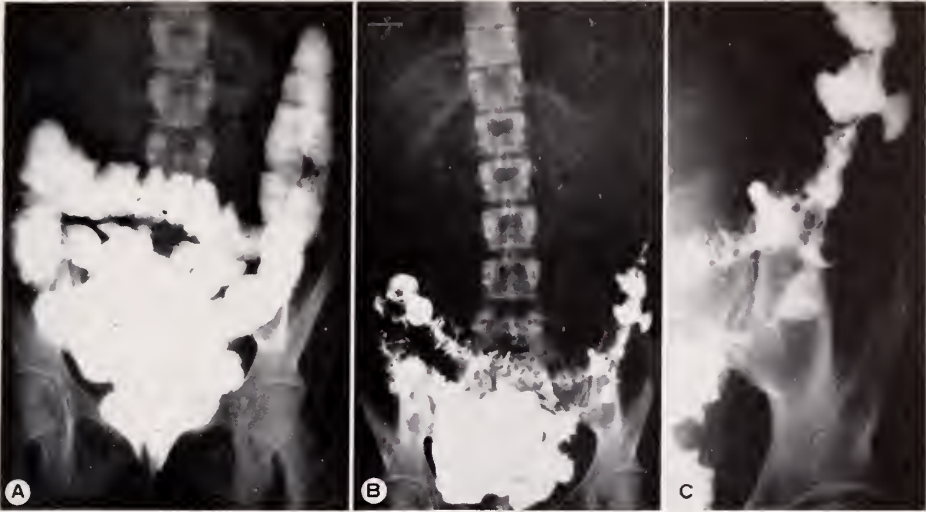


FIG. 62A. Granulomatous colitis. There is minimal involvement of the right side of the colon to the splenic flexure with irregularity of the contours and small nodular defects. The findings are more marked in distal transverse colon. There is some lack of distensibility and rigidity.

FIG. 62B. Same case as Fig. 62A, evacuation film. Mucosal pattern has an irregular cobblestone appearance. Several small skip lesions, indicated by the pseudodiverticula, are identified. Involvement of left side of colon seen on this film.

FIG. 62C. Spot film of Fig. 62B. Nodular, cobblestone, rope-like configuration of the mucosal pattern is again seen associated with multiple small pseudodiverticula.



FIG. 63. Evacuation film in granulomatous colitis. Nodular cobblestone configuration typical of granulomatous colitis is seen.



FIG. 64. Granulomatous ileocolitis. Marked cobblestoning, produced by the longitudinal and transverse ulcerations, with narrowing and rigidity of the colon. Rectum is normal. The involvement of the ileum was seen simultaneously with the involvement of the colon. This has been true in most of our cases.

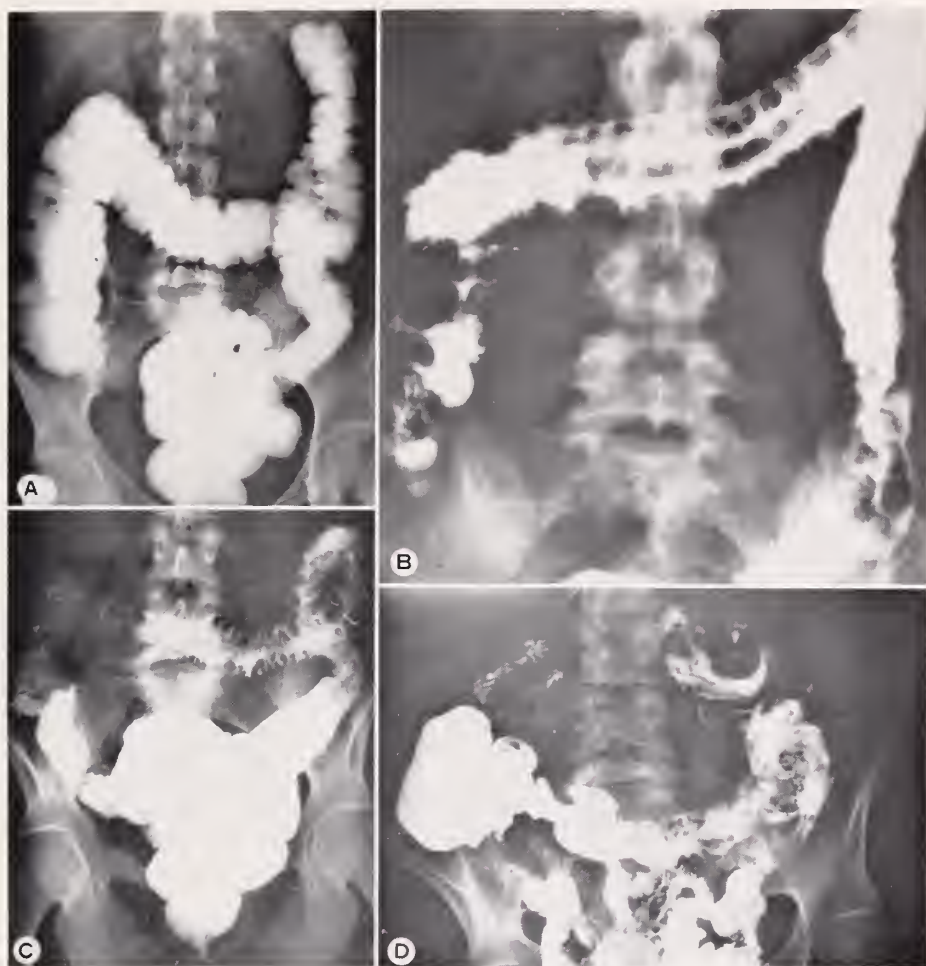


FIG. 65A. Granulomatous ileocolitis. Minimal flattening of the haustral markings of the right colon and the proximal descending colon. Rectum and sigmoid appear normal.

FIG. 65B. Same case as Fig. 65A, six months later. There are marked longitudinal and transverse ulcerations.

FIG. 65C. Same case one year after original study. There is extensive ulceration of the transverse colon with numerous and marked transverse ulcerations. Terminal ileum is also involved. Rectum, sigmoid and lower descending colon are normal.

FIG. 65D. Same case two years after original study. There is more extensive involvement with a fistulous communication between the splenic flexure and the stomach. Distal transverse colon is markedly ulcerated with gross irregularity and distortion of the contour. Marked involvement may occur in a relatively short period of time.



FIG. 66. Granulomatous ileocolitis. Characteristic intramural sinus tracts and fistulae extending from the terminal ileum to right side of colon. These tracts are typical of granulomatous disease.

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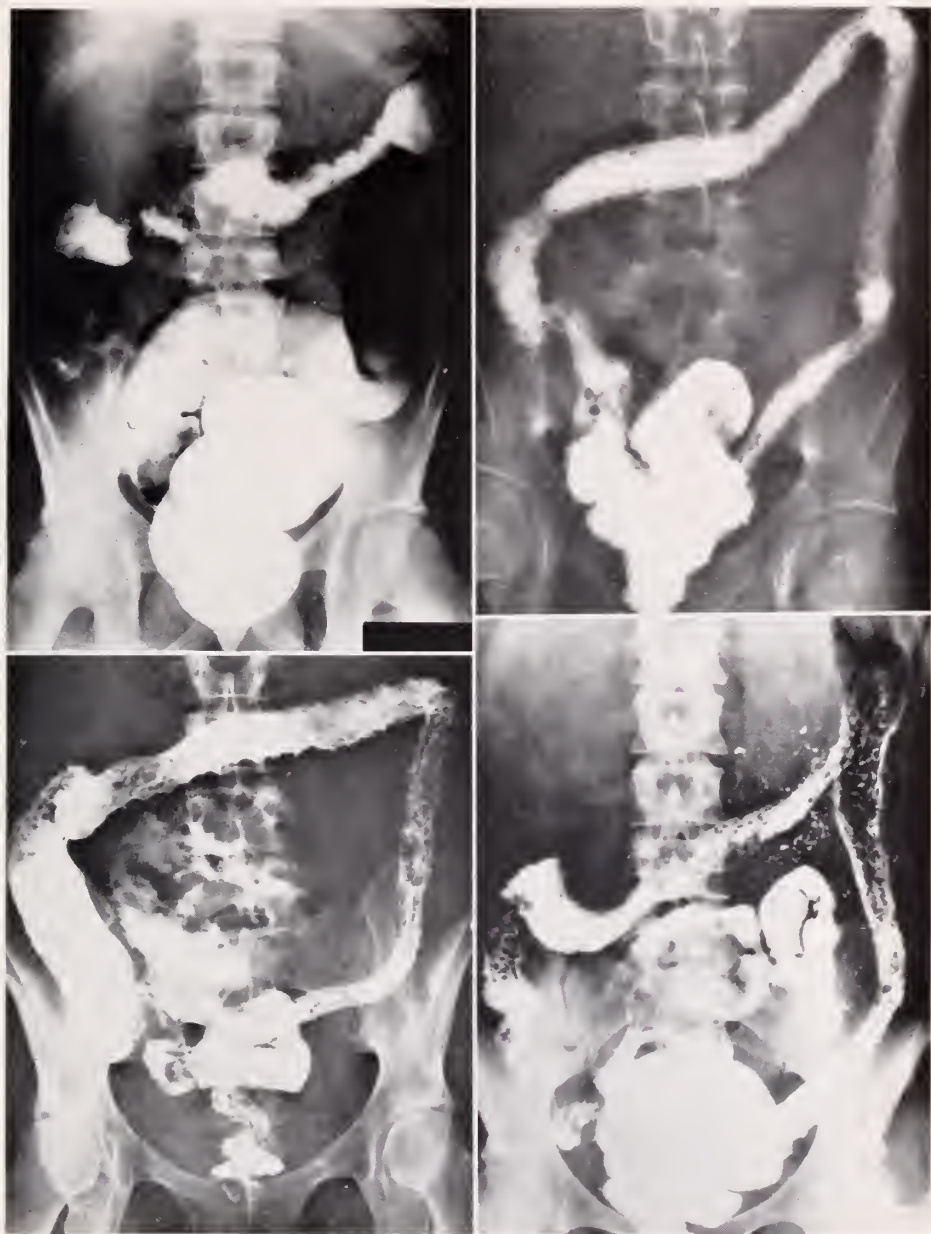
FIG. 67. Granulomatous colitis. Marked segmental involvement of colon with a large irregular ulceration in midtransverse colon.

FIG. 68. Granulomatous ileocolitis. Moderate degree of narrowing and rigidity of the entire colon with ulceration of the mucosa and numerous small inflammatory polyps. This type of diffuse involvement can be seen in both ulcerative and granulomatous colitis. Involvement of the terminal ileum with typical regional enteritis enables the radiologist to make a diagnosis of granulomatous ileocolitis.

FIG. 69. Granulomatous ileocolitis. Diffuse ulceration of the entire colon. There is a perforation of the terminal ileum with a large fistulous communication. This finding is associated with granulomatous disease rather than ulcerative colitis.

FIG. 70. Granulomatous ileocolitis. Again the findings in the colon could be those of ulcerative or granulomatous colitis. The findings in the ileum, with fistula formation, marked narrowing and rigidity, are those of regional enteritis and therefore the process is granulomatous ileocolitis.





FIGS. 67-70



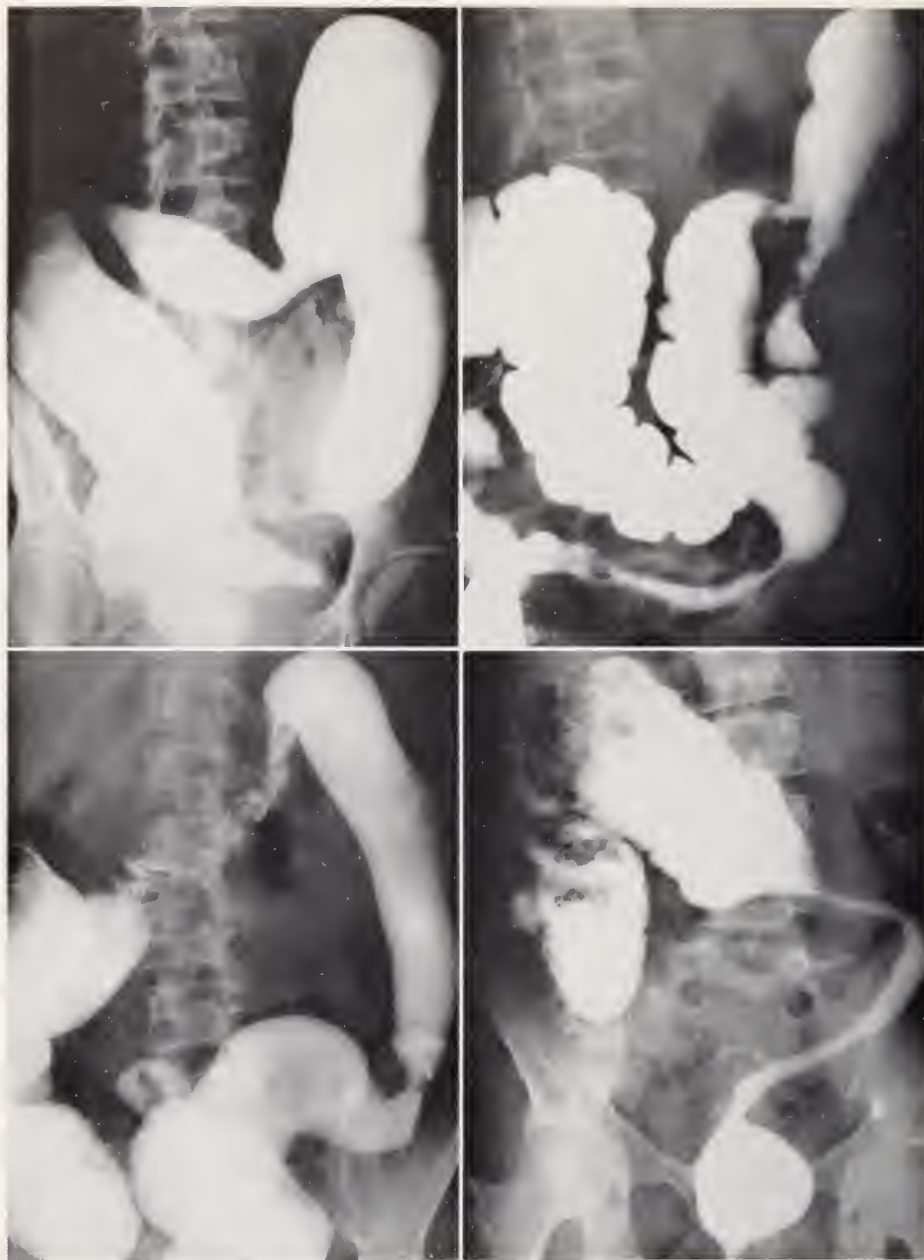


FIG. 71. Granulomatous ileocolitis. Multiple smooth strictures in granulomatous ileocolitis. To the present time these strictures have not been associated with a carcinoma.

FIG. 72. Granulomatous colitis. Multiple strictures characteristic of granulomatous colitis.

FIG. 73. Granulomatous colitis. Distal half of the transverse colon is narrowed. Another short segment of narrowing is seen in mid-descending colon. In the absence of granulomatous disease elsewhere differentiation of the latter lesion from a carcinoma would be difficult.

FIG. 74. Granulomatous colitis. Marked shortening and narrowing of the left side of the colon. Rectum is also involved.



FIG. 75 A and B. Granulomatous colitis. Involvement of the entire colon with an inflammatory process and a stricture in the sigmoid. Differentiation of this case from a carcinoma in ulcerative colitis is difficult. The evacuation film, however, reveals definite involvement of the terminal ileum with granulomatous disease, indicating that the stricture is probably benign. Clinical features were those of granulomatous colitis.



FIG. 76. Granulomatous colitis. There is a single stricture involving the right side of the colon. Differentiation of this lesion from a carcinoma is impossible.



FIG. 77. Granulomatous ileocolitis. The alterations in the colon simulate burnt-out ulcerative colitis. Presence of a fistula in the terminal ileum, however, is characteristic of regional enteritis. The findings in the colon therefore are due to granulomatous disease.



FIG. 78. Ileostomy dysfunction. Ileum proximal to the stoma is slightly dilated with increased secretions and slight irregularity of the contour. No evidence of narrowing or rigidity. The findings here are due to obstruction at stoma.



FIG. 79. Granulomatous ileitis following ileostomy for granulomatous ileocolitis. Ileum adjacent to the ileostomy is narrowed and rigid. The findings here are in contrast with the findings seen in ileostomy dysfunction and are due to extension of the granulomatous process following surgery.



### Serial X-ray Films Demonstrate the Progression of Granulomatous Disease In One Patient Following Surgical Intervention



FIG. 80. Granulomatous ileocolitis (5/22/53). Terminal ileum, distal two-thirds of transverse colon and proximal third of descending colon are involved.

FIG. 81. One year later, (5/13/54). Findings are essentially unchanged from the previous examination.

FIG. 82. Same case, evacuation film (5/13/54). Nodular irregular pattern of granulomatous disease is noted in the involved segments of small bowel and colon. Extent of inflammatory disease is often better demonstrated on a motility or evacuation film.

FIG. 83. One month status following ileo-ascending colostomy and colocolostomy (7/9/54). New terminal ileum and remaining segments of colon are normal.

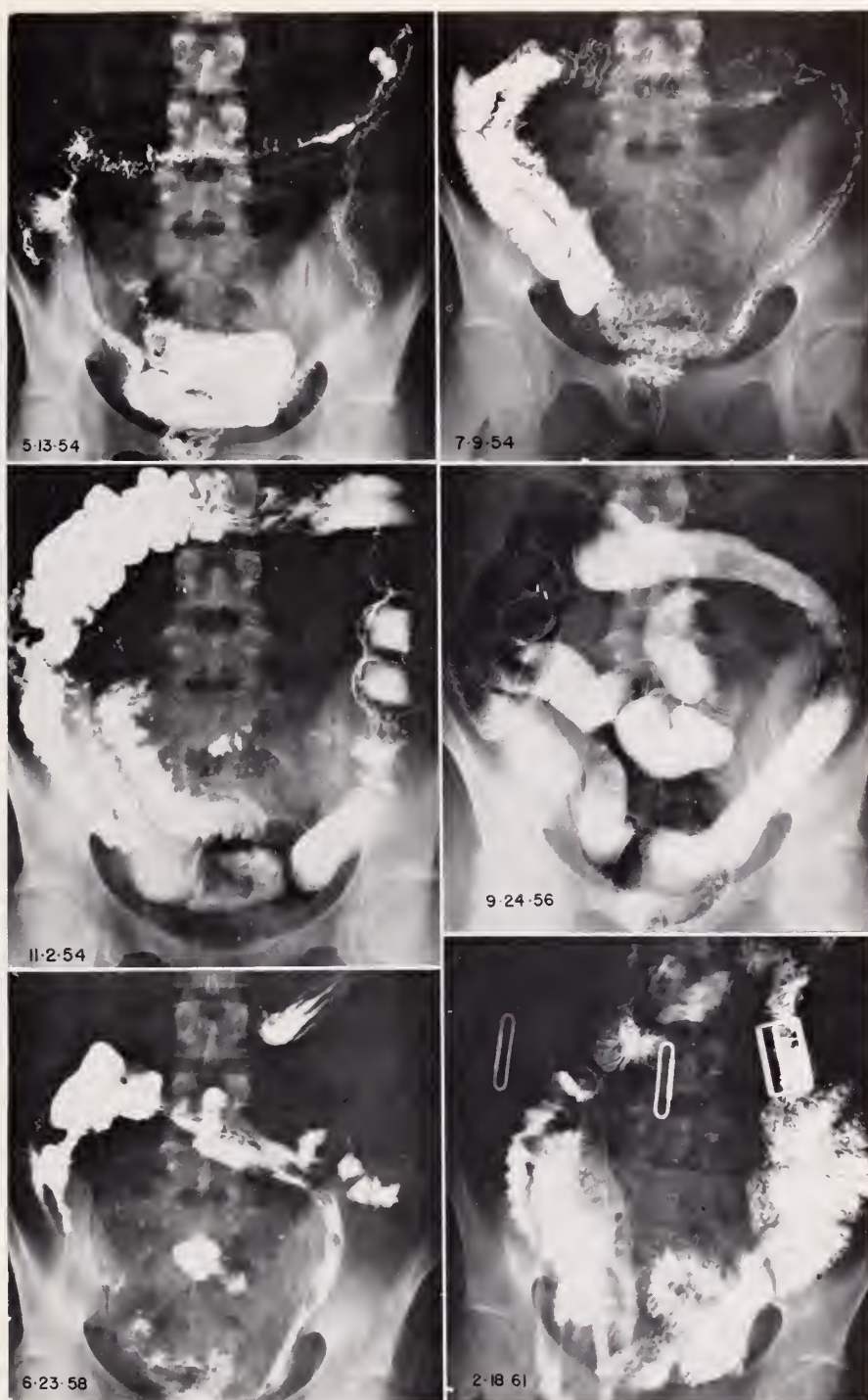
FIG. 84. Recurrent granulomatous ileocolitis (11/2/54). Four months after surgery there is recurrence in the ileum adjacent to the anastomosis and in the colon.

FIG. 85. (9/24/56). Two years later the inflammatory process in the ileum and colon is more marked.

FIG. 86. (6/23/58). Four years after surgery there is a considerable degree of narrowing, rigidity and shortening of new terminal ileum and the colon. Inflammatory polyps are also noted.

FIG. 87. One year following ileostomy and colectomy (2/18/61). Recurrent inflammatory disease in ileum adjacent to the stoma.





FIGS. 82-87

The roentgen findings in ileostomy dysfunction and granulomatous prestomal ileitis differ. In ileostomy dysfunction the ileum is dilated with considerably increased secretions. The folds are slightly thickened and ulcerations are minimal and difficult to identify (Fig 78, 79). When prestomal granulomatous ileitis develops, however, the roentgen findings are identical to those described previously for regional enteritis (Fig 80).

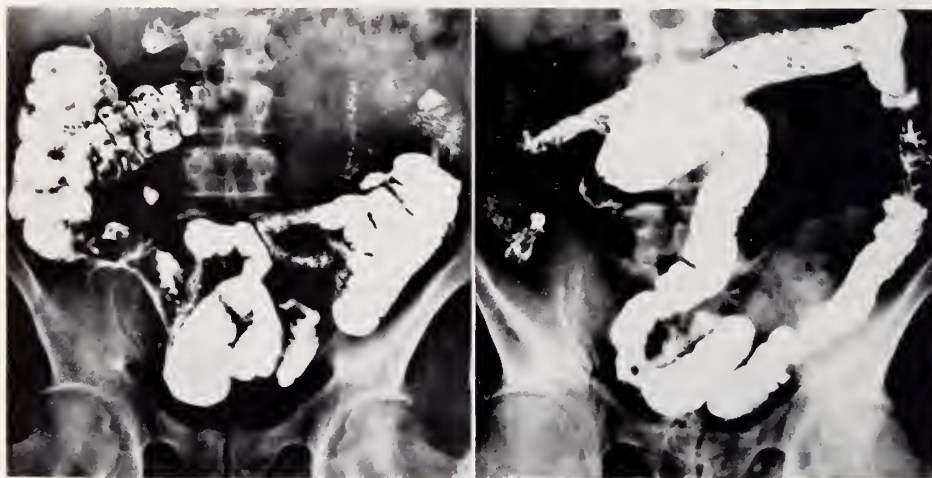


FIG. 88. Regional enteritis with numerous sinus tracts extending into mesentery.

FIG. 89. Same case as Fig. 88, recurrence after surgery. Four months after ileotransverse colostomy there is recurrence in the transverse colon. Recurrence is more likely following resection when ulceration and fistulae are prominent preoperative features of the disease.

#### REFERENCES

1. Marshak, R. H., Korelitz, B. I., Klein, S. H., Wolf, B. S. and Janowitz, H. D.: Toxic dilatation of the colon in the course of ulcerative colitis. *Gastroenterology*, 38: 165, 1960.
2. Marshak, R. H., Bloch, C. and Wolf, B. S.: The roentgen findings in strictures of the colon associated with ulcerative and granulomatous colitis. *Am. J. Roentgenol.*, 90: 709, 1963.
3. Marshak, R. H., Moseley, J. E. and Wolf, B. S.: The roentgen findings in familial polyposis with special emphasis on differential diagnosis. *Radiology*, 80: 374, 1963.
4. Marshak, R. H. and Gerson, A.: Cathartic colon. *Am. J. Digest. Dis.*, 5: 724, 1960.
5. Lindner, A. E., Marshak, R. H., Wolf, B. S. and Janowitz, H. D.: Granulomatous colitis. A clinical study. *New England J. Med.*, 269: 379, 1963.
6. Janowitz, H. D., Lindner, A. E. and Marshak, R. H.: Granulomatous colitis. *J.A.M.A.*, 191: 825, 1965.
7. Lockhart-Mummery, H. E. and Morson, B. C.: Crohn's disease of the large intestine. *Gut*, 5: 493, 1964.
8. Lockhart-Mummery, H. E. and Morson, B. C.: Crohn's disease (regional enteritis) of the large intestine and its distinction from ulcerative colitis. *Gut* 1: 87, 1960.
9. Williams, W. J.: Histology of Crohn's syndrome. *Gut* 5: 510, 1964.
10. Wolf, B. S. and Marshak, R. H.: Granulomatous colitis (Crohn's disease of the colon); roentgen features. *Am. J. Roentgenol.*, 88: 662, 1962.

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## Granulomatous Colitis: An Attempt at Clarification

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Non-specific ulcerative colitis, a distinct clinical entity, has been known to us for over a hundred years as an ulcerative disease originating in and involving the distal rectosigmoid area and to an extent the proximal colon. This is not a granulomatous disease; even when in its most extensive and severe form it crosses the ileocecal valve and invades the distal ileum, the reflux involvement of the distal small bowel is ulcerative and *not* granulomatous.

Right-sided or segmental colitis is an entirely different type of disease probably caused by a similar though in other ways different etiologic agent. Segmental colitis is characterized essentially by its tendency to produce a granulomatous type of inflammatory proliferative disease in the more proximal colon.

Since 1932 (1) we have been familiar with granulomatous disease of the small bowel, under the title of regional ileitis with its tendency to fistula formation, internal and external, perirectal infection, abdominal mass, intestinal obstruction and gross hemorrhage. The original description which regarded the disease as confined to the lowermost segment or segments of the small bowel was soon corrected since it was demonstrated that in approximately 17 per cent or more of cases the granulomatous disease did pass over the ileocecal "barrier" to produce a form of combined ileo-colitis. But this disease is and remains essentially a granulomatous disease of the small bowel (2, 3).

In 1930 Bargen and Weber (4) published a series of cases under the title "Regional migratory chronic ulcerative colitis"; in 1938 Crohn and Berg (5) described a syndrome: "Right-sided (regional) Colitis", both authors implying that this was a form of colitis or ulcerative colitis differing from the conventional rectosigmoid type only in so far as the disease emanated from the right not the left colon, involved the proximal colon either in a patchy localized predominately right-sided anatomical distribution or involved a continuous distal extension from proximal colon to distal sigmoid.

With increasing experience it was soon recognized that in over 80 per cent of "right-sided cases" the terminal ileum was extensively involved as a truly granulomatous process (combined ileo-colitis) (6, 7).

In the last decade British clinicians and other pathologists (8) have continually emphasized that what in this country we were calling "segmental colitis" was truly a granulomatous disease identical or similar to the familiar type of regional ileitis and that this "right-sided" disease was not ulcerative but was truly granulomatous in nature (9, 10).

Many of us, myself in particular, altered opinion slowly, hesitating to admit that the segmental were truly granulomatous in nature. But over the course

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of years and with more extensive study on the part of the pathologist, it would seem that not only because of fact, but also in the interest of simplification one must accept as truly granulomatous disease all cases of so-called right-sided colitis. This is particularly true since we now realize that in over 40 per cent of the cases the diseases extended into and was continuous with an identical granulomatous process in the ileum. Therefore the term "granulomatous colitis" should be accepted as a class term to cover not only the anatomically isolated forms of right-sided colitis, but also the combined forms of ileitis and colitis (ileo-colitis) or the combined forms of predominantly colitis and ileitis (colo-ileitis).

*Anatomical Distribution of the Various Types of Granulomatous Colitis*

The relative frequency of these inflammatory intestinal diseases may be generally surmised from our personal experience in consultation practice over the course of many years. Our files include to date approximately 1800 cases of non-specific ulcerative colitis; almost 1000 cases of regional ileitis and 291 cases of segmental granulomatous disease of the colon. It is evident that the incidence of granulomatous disease of the colon is relatively low compared both to ulcerative colitis and to regional ileitis.

The anatomical distribution of the pathological process in the 291 cases of granulomatous colitis was as follows:

Ascending colon alone	18 cases	} (Fig. 1)
Hepatic flexure (and transverse colon)	42 cases	
Splenic flexure (isolated form)	14 cases	
Entire proximal colon to sigmoid	91 cases	(Fig. 2)
Combined ileo-colitis, both ileum and colon extensively involved	126 cases	(Fig. 3)
Total		291 cases

Recent and more extensive knowledge of the pathology of acute regional ileitis may explain the sequence and transition from acute to chronic granulomatous disease. Until recently we had never had in our possession sections and stained slides of the pathology of acute regional ileitis. In one recent experience (courtesy of Princeton Hospital), a resection of the terminal ileum was performed under the mistaken impression that the surgeon was dealing with a neoplastic process. The pathology was that of an acute suppurative necrotizing inflammation of such severity that the acutely inflamed small bowel had perforated. Perforation occurred in eight of my more recent series (42 cases) of acute ileitis.

In a second fulminating acute case (courtesy of Bethesda Naval Hospital), two operations (resections) had been performed within two weeks. The sections of the small bowel at the first operation showed acute suppurative necrotizing inflammation characterized by infiltration with predominately polymorphonuclear leucocytes, lymphocytes, histiocytes, plasma cells and reticulocytes; there was no sign of granulomatous change. The sections obtained

at exploration two weeks later showed beginning changes characteristic of granulomatous disease.

It would seem that the pathological process in the fulminating acute case is initially one of suppuration and necrosis and that the granulomatous build-up begins almost immediately and extends progressively for the duration of the disease. The granulomatous process constitutes a continuous attempt on the part of the intestine to delimit the disease and prevent its anatomical spread by the formation of granulomatous and lymphoid barriers (11).

By contrast the more familiar acute fulminating ulcerative colitis with predominant rectal and distal colon involvement never becomes granulomatous.

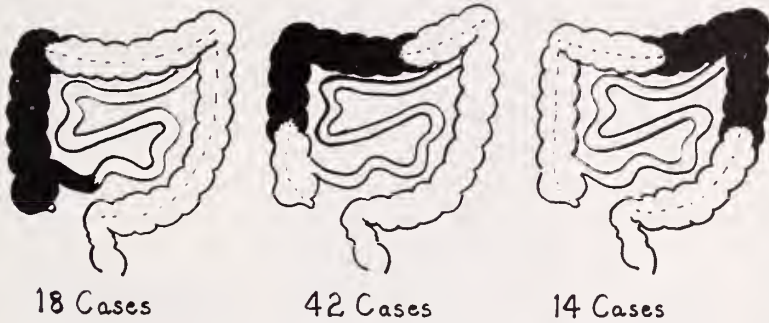
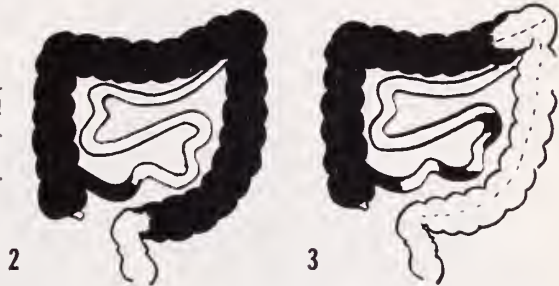


FIG. 1. Segmental Colitis: proximal colon. Seventy-four cases.

FIG. 2. Colo-Ileitis: entire proximal colon to sigmoid; very limited involvement of terminal ileum. Ninety-one cases.

FIG. 3. Ileo-Colitis (Combined). One hundred twenty-six cases.



Even with toxic dilatation of the proximal colon and even in the 24 per cent of the severest group of ulcerative colitis in which the terminal ileum becomes involved, the ileum remains ulcerative and never granulomatous.

The isolated or segmental forms of granulomatous colitis are also of interest. The pure type involving only cecum and ascending colon (18 cases), the involvement of only hepatic flexure and transverse colon (42 cases) plus the instances of isolated involvement of the splenic flexure (14 cases) together barely total 25 per cent of the anatomic distribution (Fig 4).

The next more common type consists of 91 cases of granulomatous colitis or ileo-colitis in which the entire colon from ileocecal valve to rectosigmoid area is continuously involved (Fig 5, 6). The most interesting fact here is that even when observed for years this process will not pass the recto-



sigmoid area. It would almost appear that the rectosigmoid area constitutes a barrier to the progression of the pathological process provided no surgery is performed. Why the lesion halts at this nodal point is difficult to un-



FIG. 4. Radiograph. Involvement of proximal colon ascending to mid-transverse colon.

FIG. 5. Radiograph. Colo-Ileitis: entire colon to sigmoid-involvement of entire distal ileum.

FIG. 6. Radiograph. Entire proximal colon to mid-descendens.

FIG. 7. Radiograph. Granulomatous Colitis involving mainly sigmoid and rectum.

derstand. By analogy megacolon or Hirschsprung's disease spares the rectum and beginning at this nodal point involves the proximal colon for varying extents. Perhaps a myenteric sympathetic ganglion plexus controls this area

just as achalasia represents a disordered regulation of the myenteric plexus at the esophago-cardia junction.\* If the entire proximal colon be resected and the ileum be anastomosed to the sigmoid, in 50 per cent of these cases the previously normal rectum now becomes the seat of a severe ulcerative colitis. In the past we had always considered this involvement of the rectum to be ulcerative and hemorrhagic as seen by sigmoidoscopy and biopsy—a fact which led to the belief that the rectum and rectal membrane were immune to the granulomatous type of disease. However, in the ulcerative and granulomatous forms of disease rectal and perirectal abscesses and fistulas and rectovaginal fistulas occurred in approximately 37 per cent of the cases. These rectal complications were thought to be purely suppurative in nature and not granulomatous. So too the postoperative recurrence of the disease in the rectal segment has had the appearance of simple inflammatory involvement. However Lockhard-Mummery and Morson (12) have recently demonstrated cases of true granulomatous disease of the rectum and perirectal tissues. The concept that the rectum is absolutely immune to granulomatous disease must therefore be modified to “relatively” rather than absolutely immune. In a later publication (13) the same authors recount three cases in which the rectum and the rectal ampulla *only* were involved in granulomatous disease; and further state that in their experience the rectum was involved with granulomatous or sarcoid disease in 50 per cent of the cases (Fig 7).

In classical regional terminal ileitis fistulas from the ileum to the sigmoid constitute a frequent form of internal fistulization. In two of our recent cases while attempting to resect the ileitis, it was necessary because of multiple fistulas to resect the area of the sigmoid involved with these fistulas. The resected sleeve of sigmoid was definitely granulomatous in nature constituting an implantation by direct extension (Fig 8).

The final form of granulomatous colitis comprises 126 cases of “combined ileo-colitis” wherein both extensive areas of the distal ileum and extensive areas of the proximal colon are simultaneously involved in most typical granulomatous disease. Because of the predominance of areas of colonic involvement the suggestion has been made that this type be called “colo-ileitis”, but this would seem only to compound an already overburdened nomenclature.

The symptoms of this type of combined ileo-colitis or colo-ileitis are identical with those that characterize the disease group as a whole, namely fever, severe diarrhea and abdominal pain, internal fistulous tracts from ileum to colon or on rare occasions to transverse colon, to ileum or even to duodenum and the usual incidence of rectal suppurative complications.

#### *Etiological and Clinical Considerations*

Of what clinical and prognostic significance is the fact that regional or segmental colitis is granulomatous rather than ulcerative in its pathological

\* Recently, in Brazil, I have seen radiographic films of cases of Chagas's disease. In this disease the entire colon is represented as a megacolon and similarly the esophagus is dilated as a megaesophagus.

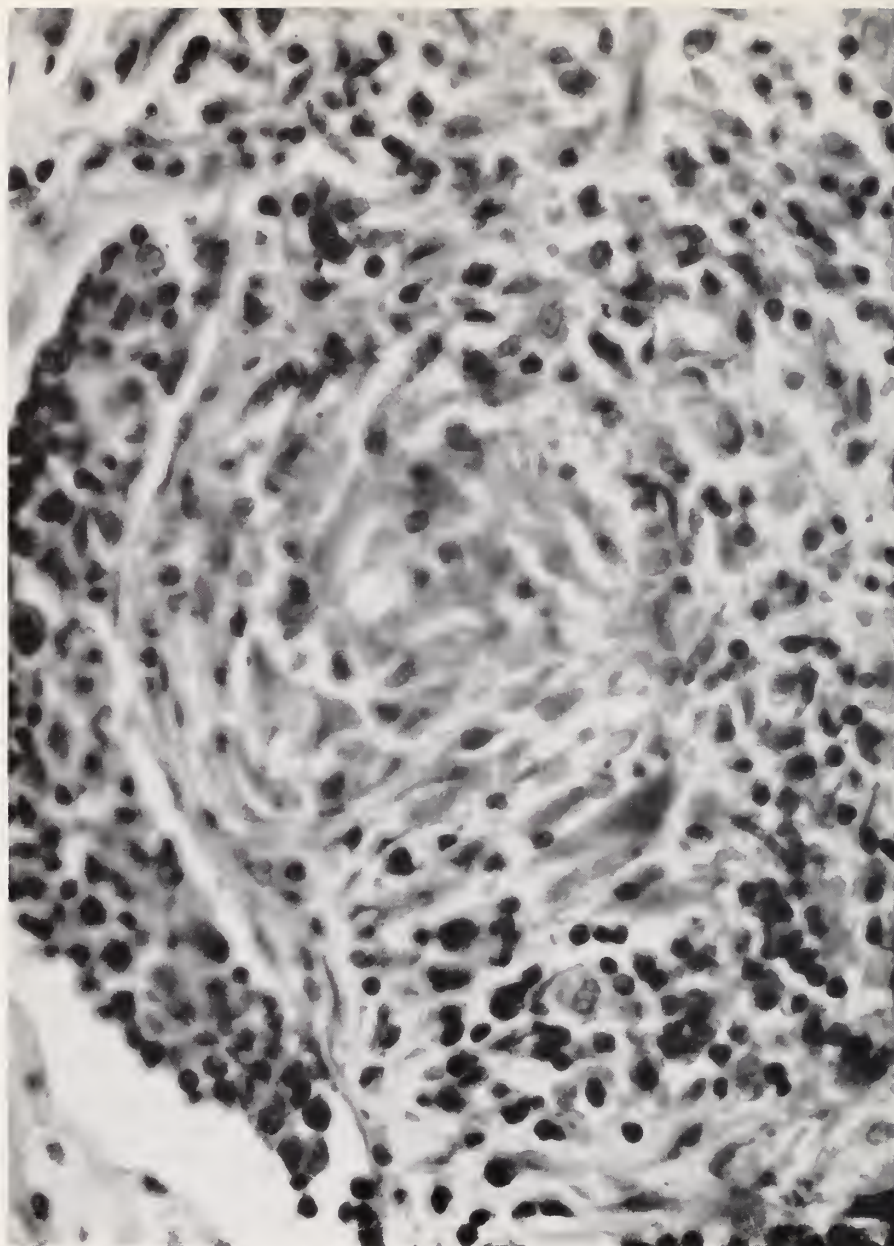


FIG. 8. Histology of granulomatous colitis, granulomatous ileo-colitis, sarcoid reaction. Giant-cells at mid left area and lower right ( $\times 800$ ).

basis? From the etiologic point of view few if any differences are to be observed. The age incidence, the onset of both types at the average age of 27 years and the equal involvement of the sexes is common to both. Segmental colitis is relatively a more mild form of the granulomatous diseases. The diar-



rhea is less severe, the fever, so-called "fever of unknown origin," may continue for years before the fever and diarrhea are associated. The same applies to the joint and arthritic manifestations and to eye complications (iritis, iridocyclitis, corneal ulceration). In many of these cases the distal constitutional manifestations are severe and noteworthy, and the milder diarrhea and intestinal symptoms lead to many lapses of diagnosis. Granulomatous colitis only occasionally creates internal intestinal fistulas or fistulas to the abdominal wall in contrast to regional ileitis in which they are so common. In both ulcerative colitis and granulomatous colitis erythema nodosum is common; dermatitis gangrenosum we have seen only in ulcerative colitis. Both forms interfere with menstruation causing amenorrhoea at the height of the clinical activity. Both types retard growth in the prepubertal child, cause stunted height, delay menses and delay pubertal maturation. Granulomatous colitis is not psychosomatic in our viewpoint nor does it demonstrate a familial tendency such as is so often encountered in regional ileitis; occasionally one observes a crass example of ileitis and of granulomatous colitis in siblings or in more than one person of a close membership family. Liver dysfunction was seen only once in this series of cases.

Granulomatous colitis appears to have a better prognosis than ulcerative colitis and probably better than that of regional ileitis. The toxicity of granulomatous colitis is less; the anatomical pathological process is more circumscribed. Corticosteroid therapy appears to be more effective thus reducing the need for local surgical resection. Gross hemorrhage is more common in granulomatous colitis, the hemorrhage being extreme and originating not from any vessel or vessels but from the entire hemorrhagic mucosa. In this series gross hemorrhage occurred in 26 cases (9 per cent) in comparison with ileitis (4.6 per cent).

### *Treatment*

In the years before corticosteroid therapy many cases of localized granulomatous colitis were subjected to partial colonic resection with good results and with no recurrence. To a greater extent than either regional ileitis or ulcerative colitis granulomatous colitis appears to be amenable to corticosteroid therapy. This applies particularly to the localized or right-sided segmental forms which react favorably to corticosteroid therapy with rapid control of diarrhea, cessation of fever and return of appetite and weight. The excellent and prompt result with corticosteroid therapy, in many instances with radiographic demonstration of healing and disappearance of the granulomatous areas, has made surgical intervention unnecessary in a large percentage of cases.

The corticosteroid therapy consists of prescribing by mouth prednisone 5 mgm 4 to 6 times daily. We find little or no benefit in prescribing the many commercial variations of the proprietary prednisones; these are more expensive and offer no advantages except perhaps in unusual cases of drug intolerance. In febrile cases or where immediate results are mandatory be-

cause of the severity of the disease, the oral steroids should be supplemented by intramuscular injections of soluble ACTH such as ACTH gel or zinc corticotropin 40 units daily for several days and then intermittently in diminishing frequency as clinical improvement is achieved. This type of corticosteroid therapy is safe, peptic ulceration very unusual (four times in the course of years); intestinal perforation was not encountered. Corticosteroids in moderate doses may be continued for long periods of time without untoward reactions. A rise of blood pressure is very unusual; glycosuria has in this series never been encountered, nor has osteoporosis been observed.

The oral administration of cortisone products must be continued over long periods of time in diminishing dosage as improvement is achieved. Even very small doses of cortisone, 5 to 10 milligrams of prednisone, should be continued indefinitely as maintenance dosage to prevent recurrence of symptoms. In the advanced or combined cases no claim for "cure" can be made, but as palliative treatment the corticosteroids are unsurpassed. In some of the regional or localized segmental forms even "cure" as checked by radiographic examination can occasionally be demonstrated. Antibiotics are rarely employed except for suppurative complications. The diet may be general and liberal; much physical rest is essential. Psychotherapy may be helpful in persons with complex personal problems, but is not curative.

In those cases which do not respond to this type of therapy and in which the lesion progresses to the rectosigmoid area with persistence of active symptoms surgical intervention becomes mandatory. A two-stage procedure, subtotal resection of the entire colon down to the sigmoid with a temporary sigmoid colostomy, or a one-stage colectomy and ileosigmoidostomy is the procedure of choice. Unfortunately in approximately 50 per cent of the cases reported in 1947 (14) immediate or eventual involvement of the rectum took place. In such cases permanent ileostomy is the only choice and gives a good result with a continued normal life span.

In our experience we have observed only two instances of carcinoma of the colon (distal transverse segment) complicating a case of granulomatous colitis. This is in contrast to the high incidence of carcinoma as a complication of ulcerative colitis.

The recent report of a case of multiple carcinoma of the colon in ulcerative colitis with a definite carcinoma in the terminal ileum is very exceptional but only confirms the impression that the back-wash of reflux ileitis of universal colitis is ulcerative in nature and not granulomatous (15).

### *Prognosis*

It is essential to gain some general impression of the prognosis in granulomatous colitis, particularly the end results of conservative medical versus radical surgical procedures. The following tables are based upon a conscientiously attempted but nevertheless incomplete follow up of cases since 1938; the material is from private practice, much or most of it referred, frequently from distant geographical areas and hence difficult to trace. The



follow up covers approximately 70 per cent of the total registered cases to date regardless of age, sex or associated diseases. All cases were treated in the same manner with corticosteroid therapy.

In the localized proximal forms involving ascending and transverse colon (Table I) one gains the impression of a relatively benign disease with a fairly high percentage of "cure" or durable improvement (24 of 34 cases). Those cases in which resection was performed reported an excellent and permanent result.

The more severe type of granulomatous colitis with diffuse, subtotal involvement to or including the sigmoid gives a far more serious prognosis.

TABLE I  
*Therapeutic Results: Partial Follow Up*

	Cases
<i>Ascending Colon</i>	
Medical Treatment	
Well .....	18
Surgical Treatment	
Well .....	5
Poor .....	1
Died (Carcinoma) .....	1
	—
	25
<i>Transverse Colon</i>	
Medical Treatment	
Well .....	6
Surgical Treatment	
(Recurrence)	
Well .....	2
Died .....	1
	—
	9
<i>Total</i>	34 Cases
	2 Deaths

Medical treatment here has its limitations (Table II); only 17 of 73 cases being reportedly "well" or continuing to live an active life free of symptoms. This too is very gratifying and often quite surprising. The remaining 50 of the 73 cases had by necessity recourse to surgical intervention. The operation of choice is a subtotal colectomy with ileosigmoidostomy, the procedure being performed in one or in two stages. The follow up findings of resection in these cases are fair, approximately 70 per cent of the survivors doing well or very well although the surgical mortality rate is high and life often is saved only by recourse to permanent ileostomy (20 cases).

In the final and largest group (Table III) comprising the cases with extensive disease of both colon and ileum (combined ileo-colitis) the prognosis is again seen to be grave. Medical treatment was less successful and was possible only in the few relatively mild cases and those free of fistulous, sys-

temic or other complications. The surgical treatment; radical resection or occasionally short-circuiting operations, is often most satisfactory even though the operative mortality is high and permanent ileostomy represents the final life-saving measure in a large percentage of the cases (20 per cent).

TABLE II  
*Therapeutic Results: Partial Follow Up*

	Cases
<i>Subtotal Colitis-Colo-Ileitis</i>	
Medical Treatment	
Well .....	17
Poor .....	3
Died (Uremia, Cirrhosis, fulminating diseases) .....	3
Surgical Treatment	
(Including ileostomy 20)	
Well .....	35
Poor .....	5
Died .....	10
<i>Total</i>	73 Cases 13 Deaths

TABLE III  
*Therapeutic Results: Partial Follow Up*

	Cases
<i>Combined Ileo-Colitis</i>	
Medical Treatment	
Well .....	20
Improved .....	2
Poor .....	3
Died .....	2
Surgical Treatment	
(Including: resections 50; short-circuit 10; ileostomy 12)	
Well .....	43
Improved .....	3
Poor .....	6
Died .....	8
<i>Total</i>	87 Cases 10 Deaths

#### SUMMARY

The general impression from even an incomplete follow up study is that conservative treatment of granulomatous colitis is successful in approximately only twenty per cent of cases. Yet the occasional brilliant and striking therapeutic effect of conservative therapy particularly in the proximal forms as shown (though rarely) by radiographic evidence of reversal of the disease process certainly speaks for a fair and extended trial.

The remaining cases represent obvious failures of medical treatment. Operation is indicated mainly for massive hemorrhage, protracted fever, systemic manifestations, perirectal fistulas or for intractability in general.

The surgical mortality rate is high and the fact that ileostomy is so often the eventual recourse calls for considerate and deliberate judgment when advocating radical surgical therapy.

## REFERENCES

1. Crohn, B. B., Ginzburg, L., and Oppenheimer, G. D.: Regional ileitis; pathologic and clinical entity. *J.A.M.A.*, 99: 1323, 1932.
2. Colp, R.: Case of non-specific granuloma of terminal ileum and cecum. *S. Clin. North America*, 14: 413, 1934.
3. Crohn, B. B., and Rosenak, B. D.: Combined form of ileitis and colitis. *J.A.M.A.*, 106: 1, 1936.
4. Bagen, J. A., and Weber, H. M.: Regional migratory chronic ulcerative colitis. *Surg. Gynec. & Obst.*, 50: 964, 1930.
5. Crohn, B. B., and Berg, A. A.: Right-sided (regional) colitis. *J.A.M.A.*, 110: 32, 1938.
6. Yarnis, H., Marshak, R. H., and Crohn, B. B.: Ileocolitis. *J.A.M.A.*, 164: 7, 1957.
7. Yarnis, H. and Crohn, B. B.: Segmental (ulcerative) colitis. *Gastroenterology*, 38: 721, 1960.
8. Neuman, H. W., and Dockerty, M. B.: Pathology of regional (segmental) colitis. *Surg. Gynec. & Obst.*, 99: 572, 1954.
9. Brooke, B. N., and Cooke, W. T.: Ulcerative colitis: diagnostic problems and therapeutic warning. *Lancet*, 2: 462, 1951.
10. Wells, C.: Ulcerative colitis and Crohn's disease. *Ann. Roy. Coll. Surgeons England*, 11: 105, 1952.
11. Crohn, B. B.: The pathology of acute regional ileitis. *Am. J. Digest. Dis.*, 10: 565, 1965.
12. Lockhart-Mummery, H. E., and Morson, B. C.: Crohn's disease (regional enteritis) of the large intestine and its distinction from ulcerative colitis. *Gut*, 1: 87, 1960.
13. Lockhart-Mummery, H. E., and Morson, B. C.: Crohn's disease of the large intestine. *Gut*, 5: 493, 1964.
14. Crohn, B. B., Garlock, J. H., and Yarnis, H.: Right-sided (regional) colitis. *J.A.M.A.*, 134: 334, 1947.
15. Brown, C. H., Diaz, R. J., and Michener, W. M.: Carcinoma of the colon and ileum in chronic ulcerative colitis with reflux ileitis. *Gastroenterology*, 47: 306, 1964.

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# Escherichia Coli 04 Hemagglutinin Production by Three Premature Infants

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It is now clear that the newborn infant when appropriately stimulated is able to produce a variety of antibodies (1). Even the prematurely born has been shown to respond to the parenteral injection of diphtheria (2) and *Salmonella* vaccines (3), to infection with an enteropathogenic *Escherichia coli* (4) and with adeno and echo viruses (5). Infection with rubella virus while in-utero leads the infant to make specific antibodies (6). However, all infectious agents are not equally good antigens and this is especially true in the neonatal period (1). If we are to understand resistance in this early period of life, we must have more data. In particular, we must know how newborn infants, full term and premature, respond immunologically to specific naturally acquired infections.

*Escherichia coli* are a part of the natural environment of the newborn infant. The frequency with which the different serotypes are encountered varies (7). The 04 serotype is not considered an enteropathogen. However it is of interest to pediatricians because of its frequent association with urinary tract infections (8). In nurseries for prematures it has been associated with epidemics of pyuria and sepsis (9, 10). It has been shown that infection with *E. coli* 04 results in the production of specific hemagglutinins by adults (11). However, we are not aware that newborns or premature infants have been investigated previously for the development of these specific antibodies.

It is the purpose of this report to present the results from a study of the development of the *E. coli* 04 hemagglutinin antibody by three premature infants, each of whom acquired an *E. coli* 04 infection while still in the hospital nursery.

## MATERIAL AND METHODS

**SERA.** Venous or cord blood was collected aseptically. The serum was separated and stored at approximately minus 20°C.

**DETECTION OF *E. coli* 04.** This was done in the Bacteriology Laboratory at the North Shore Hospital and the usual diagnostic media were employed. The *E. coli* were unique in that on human blood agar they formed medium sized moist greyish hemolytic colonies. These were identified serologically as *E. coli* 04 at the Beth Israel Hospital *E. coli* and Salmonella Center in New York City.\*

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\* Mr. I. Rothenberg of the microbiology laboratory at North Shore Hospital isolated the *E. coli* and Dr. I. D. Cocioba of Beth Israel Hospital did the typing.

ANTIGEN SOURCES. *E. coli* 04 was that recovered from Baby Z; *E. coli* 0111:B4 was obtained from Nassau County Department of Health, Bacteriology Laboratory;\* the *Staphylococcus aureus* was the Bartlett strain used by us in earlier studies (13).

HEMAGGLUTINATION TEST. The *E. coli* were grown on trypticase soy agar plates. After overnight incubation at 37°C, the growth was suspended in normal saline, 5 ml per plate, and heated in a bath of boiling water for one hour. After centrifugation for 30 minutes, the supernatant was collected and stored at 4°C for 72 hours before being used to sensitize red blood cells. This was done by exposing 10 ml of a 0.25 per cent suspension of human type O cells to 2 ml of a 1:10 dilution of the *E. coli* supernatant for 30 minutes at 37°C in a water bath. The remaining details were the same as for the staphylococcal hemagglutination test which has been described by us in an earlier report (12).

FRACTIONATION OF SERA. This was done using n, M-diethyl amino ethyl

TABLE I  
*Clinical Data from Three Premature Infants*

Patient	Sex	Birth Weight	Gestational Age		Age (& weight) when first <i>E. coli</i> 04 cultured	Symptoms at that time	Source of + culture
			M*	Weight**			
H	F	1530 gm	32 wks	31 wks	20 days (1720 gm)	Loose Stools	Nose Throat Stool
Z	F	1616 gm	...	32 wks	18 days (1480 gm)	Loose Stools Pyuria	Stool Urine
G	M	2190 gm	34 wks	34 wks	14 days (2340 gm)	Asymptomatic	Stool

\* Estimated from menstrual history.

\*\* Estimated from Lubchenco, et al, charts (14).

ether (DEAE) cellulose columns with 0.02 M phosphate buffer (pH 6.3) and 1 M NaCl as described by us earlier (12). The fractions eluted by the phosphate buffer contained immunoglobulin G (IgG, 7S) and those elicited by the 1 M NaCl contained immunoglobulin M (IgM, 19S) (13) and other serum proteins. This separation is not as clear as one that might have been obtained if an ultracentrifuge with sucrose gradients had been used. However the column technique lends itself to work in a small laboratory, and the trace amounts of contaminants which might have been present in our fractions were not considered to be enough to significantly change the results of our tests.

# RESULTS

The significant clinical details for each of the three patients are given in Table I. There were two females and one male patient. The birth weights were 1530 gm, 1116 gm and 2190 gm. The gestational ages (as estimated both from



history of last menstrual period and Lubchenco et al (14) birth weight charts) ranged from 31 to 34 weeks. Between the second and third weeks of life all were found to be harboring *E. coli* 04. One infant was asymptomatic and the other two came to our attention because of loose stools. One of these two was also found to have a urinary tract infection. None had sepsis.

The results of the serological studies are summarized in Table II. Baby H was found to have a 1:160 titer of specific hemagglutinating antibody two weeks after the first positive culture. This same titer was still present 16 weeks later. Baby Z did not have any detectable antibody two weeks after her infection was discovered, but by four weeks the titer was 1:160, by 16 weeks 1:320 and by 22 weeks 1:640. Because of persistent pyuria and bacilluria she was treated with a variety of antibiotics and eventually cleared. Baby G was found to have *E. coli* 04 in his stools during a routine survey shortly before discharge from the nursery. At that time there was no de-

TABLE II  
*Development of E. Coli 04 Hemagglutinins in Three Premature Infants*

Patient	Cord Blood	Weeks After First Positive Culture					
		0	2	4	8	16	22
H	...		160*			160	
Z	...		<20	160		320	640
G	<20	<20			80		

\* Reciprocal of highest dilution giving positive reaction.

tectable antibody. When examined eight weeks later he was still well, but his hemagglutinin titer was 1:80 and he still carried *E. coli* 04 in his stools.

Cord serum was available from only one of these three prematures, Baby G. It was free of any *E. coli* hemagglutinin. However, cord sera from 24 other infants in our nursery were also tested. Nineteen had no *E. coli* 04 titer; the remaining five had equivocal levels of only 1:20. When sera from 24 randomly selected adults were screened, 16 had titers greater than 1:200 for *E. coli* 04 hemagglutinin.

The 16 week serum from Baby H and the 22 week serum from Baby Z were fractionated on DEAE columns in order to determine the class of antibody present. All of the H serum hemagglutinin and all except for a trace of the Z serum hemagglutinin was in the 1 M NaCl fractions which contain the immunoglobulin M (IgM).

As a control for the specificity of the *E. coli* 04 reaction, the sera from all three patients were tested also with red blood cells sensitized with an extract made with *E. coli* 0111:B4 and with one made with a strain of *Staphylococcus aureus*. None reacted with the *E. coli* 0111:B4 sensitized cells. However baby Z's 22 week (5 month) specimen showed a 1:160 titer with the cells treated with staphylococcal extract. This child's earlier sera did not

agglutinate these cells. At the time the 22 week serum was collected from Z, she was recovering from an episode of pneumonitis during which a *Staphylococcus aureus* had been recovered from her throat.

#### DISCUSSION

It is clear from our investigation that prematurely born infants who acquire *E. coli* 04 from their environment can respond with the production of a specific antibody—even within the first month of life. This is in striking contrast to the immunological behavior of young infants who recover from staphylococcal pneumonia. Unless they are at least four months old they fail to produce staphylococcal hemagglutinins (12).

Our study of 24 cord sera confirmed earlier observations by Neter, et al (15) that very little *E. coli* antibody crosses the placenta. None of our cord sera had titers greater than 1:20. This may also be contrasted with our previously reported studies of staphylococcal hemagglutinins (12). Twenty-one of 28 cord sera tested for staphylococcal hemagglutinin had titers greater than 1:20. Perhaps the presence of passively acquired antibody influences an infant's ability to respond to infection. It is significant that among 37 randomly collected sera from infants under one year of age we found *E. coli* 04 hemagglutinin titers of 1:80 or greater in nine infants. Five of these infants were only three months old. In a similar survey for actively acquired staphylococcal hemagglutinin, 12 of 63 infants had titers of 1:80 or greater. However, all of these twelve were more than four months old (12). It is obviously difficult to generalize regarding the immunological responsiveness of the young infant.

There is data to suggest that the duration of *E. coli* pyelonephritis is shortened if specific antibody is present (16). Since the 04 serotype is frequently associated with urinary infections (as it was in one of our three patients) the ability of the very young infant to respond immunologically to this organism may be important.

#### SUMMARY

The immunological response to naturally acquired *E. coli* 04 infection of three infants who were born prematurely (after 31 to 34 weeks gestation) is noted. Although the infections were apparently initiated when the infants were only 2 to 3 weeks in age, significant specific hemagglutination titers were detected two and four weeks later. This antibody was shown to be in the macroglobulin (IgM) fraction by DEAE column chromatography. The prompt immunological response of these premature infants to *E. coli* 04 is contrasted to the lack of response, previously noted by us of full term newborns to staphylococcal infection.

#### REFERENCES

1. Altmeier, W. A., and Smith, R. T.: Immunologic aspects of resistance in early life. *Pediat. Clin. N. Amer.*, 12: 663, 1965.
2. Dancis, J., Osborn, J. J., and Kunz, H. W.: Studies of the immunology of the new-

- born infant IV Antibody formation in the premature infant. *Pediatrics*, 12: 151, 1953.
3. Fink, C. W., Miller, W. E., Jr., Dorward, B., and LoSpalluto, J.: The formation of macroglobulin antibodies. II Studies on neonatal infants and older children. *J. Clin. Invest.*, 41: 1422, 1962.
  4. Stulberg, C. S., Zuelzer, W. W., and Page, R. H.: *Escherichia coli* 0127:BS, A serotype causing infantile diarrhea. III The antibody response of infants. *J. Immunol.*, 76: 281, 1956.
  5. Eichenwald, H. F., and Kotsevalov, O.: Immunologic responses of premature and full term infants to infection with certain viruses. *Pediatrics*, 25: 829, 1960.
  6. Weller, T. H., Alford, C. A., and Neva, F. A.: Retrospective diagnoses by serologic means of congenitally acquired rubella infection. *New England J. Med.*, 270: 1039, 1964.
  7. Vosti, K. L., Goldberg, L. M., Monto, A. S., and Rantz, L. A.: Host parasite interaction in patients with infections due to *Escherichia coli*. I The serogrouping of *E. coli* from intestinal and extra intestinal sources. *J. Clin. Invest.*, 43: 2377, 1964.
  8. Pryles, C. V., and Glagovsky, A.: Serological characterization of *Escherichia coli*. Study in acute and recurrent urinary tract infections in infants and children. *Pediatrics*, 36: 219, 1965.
  9. Kenny, J. F., Medearis, D. N., Drachman, R. H., Gibson, L. E., and Klein, S. W.: An outbreak of urinary tract infection and septicemia due to *Escherichia coli* in male infants. *Am. J. Dis. Child.*, 104: 461, 1962.
  10. Sweet, A. Y., and Wolinsky, E.: An outbreak of urinary tract and other infections due to *E. coli*. *Pediatrics*, 33: 865, 1964.
  11. Ehrenkranz, N. J., and Carter, M. J.: Immunologic studies in urinary tract infections. I. The hemagglutinin response to *Escherichia* O antigens in infections of varying severity. *J. Immunol.*, 92: 798, 1964.
  12. Florman, A. L., Lambertson, G. H., Zepp, H., Ainbender, E., and Hodes, H. L.: Relation of 7S and 19S Staphylococcal hemagglutinating antibody to age of individual. *Pediatrics*, 32: 501, 1963.
  13. R. Ceppellini, et al.: Nomenclature for human immunoglobulins. *Bull. World Health Organ.*, 30: 447, 1964.
  14. Lubchenco, L. O., Hansman, C., Dressler, M., and Boyd, E.: Intrauterine growth as estimated from liveborn birth weight data at 24 to 42 weeks of gestation. *Pediatrics*, 32: 793, 1963.
  15. Neter, E., Westphal, O., Luderitz, O., Gino, R. M., and Gorzynski, E. A.: Demonstration of antibodies against enteropathogenic *Escherichia coli* in sera of children of various ages. *Pediatrics*, 16: 801, 1958.
  16. Sanford, J. P., and Barnett, J. A.: Immunologic responses in urinary tract infections. Prognostic and diagnostic evaluation. *J.A.M.A.*, 192: 587, 1965.

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## RADIOLOGICAL NOTES

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### CASE NO. 267

A 37-year old white male was admitted to the hospital because of right upper quadrant pain and jaundice. Past history revealed several bouts of fever, epigastric pain and obstructive jaundice four years prior to admission at which time exploratory laparotomy and biopsy had revealed constrictive choledochitis with serosal fibrosis. A liver biopsy at that time showed essentially normal liver architecture with minimal bile stasis. The common bile duct was drained via a T tube for the next six months and the patient was treated with steroids and cholegogues. Interval T tube cholangiograms showed increasing caliber of the distal common duct and the T tube was removed.

Liver chemistries during the course of the present admission showed a mild to moderate elevation of alkaline phosphatase, total bilirubin (mainly direct fraction) and transaminase which gradually returned toward normal. Cephalin flocculation remained at 2 plus. Liver biopsy revealed normal liver tissue with no evidence of bile stasis, inflammation or fibrosis.

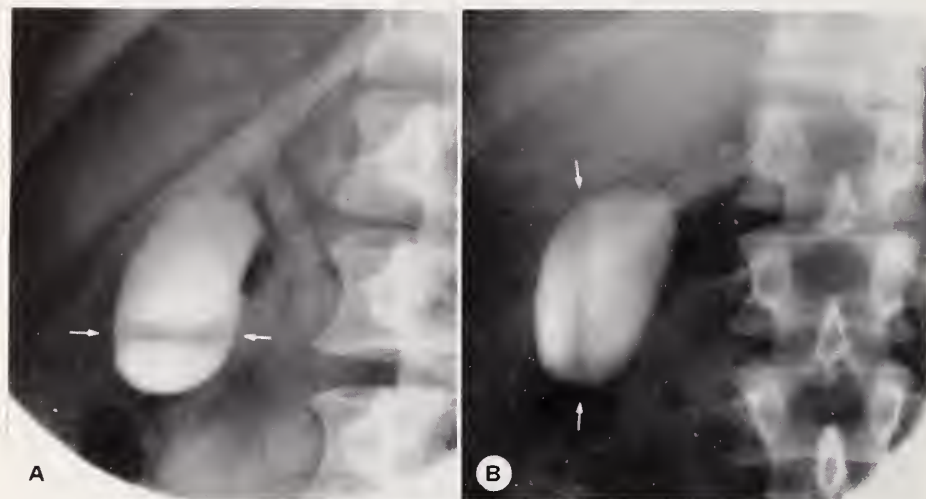
Chest X-ray showed no abnormality. Intravenous cholangiography (Cholegraffin) on admission failed to visualize the biliary system, and was repeated ten days later. At that time, the common duct system was entirely normal and visualized promptly and well. There was no evidence of obstruction and the lower end of the duct tapered smoothly with prompt passage of opaque material into the duodenum. Laminograms were included in the study. The gallbladder filled promptly during the intravenous study. Many radiographs were obtained including upright spot films and lateral decubitus projections (Fig 1a, b). All of the horizontal ray films demonstrated a broad non-opacified layer in the gallbladder which changed its location from upright to decubitus positions, and which lay between opacified bile above and below. Despite an attempt to manipulate the patient to mix the bile, this broad layer could never be obliterated. The margins of the gallbladder were smooth and the gallbladder appeared to contract after a fatty meal. Despite the use of a fine focal spot technique (1 mm) no particulate matter could be identified in the non-opacified band and a positive diagnosis of calculus could not be advanced.

The patient was treated with steroids. His hospital stay lasted ten days. In the week following discharge he was placed on a high fat diet in an attempt to empty the gallbladder thoroughly and repeatedly. Oral cholecystogram (Telepaque) was then performed. No abnormality was demonstrated in the gallbladder and the gallbladder contents were homogeneously opacified. The study included many upright compression spot films (Fig 2).

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## DISCUSSION

Radiologists are quite familiar with the use of horizontal ray technic to demonstrate tiny calculi and floating calculi, and an oral cholecystogram can be considered incomplete if a radiograph made with this technic is not included in the series. However it is not very often that the need for horizontal ray technic arises during intravenous cholangiography. When indicated it is usually because of failure of the gallbladder to visualize with previous oral



Case 267, Fig. 1A. Erect compression spot film during intravenous cholangiogram (Cholegrafin, 1 mm tube focal spot) shows gallbladder distended with opaque material in the center of which lies a layer of non-opacified material (between arrows). No particulate matter can be seen in this non-opacified layer and no stones are seen at bottom of fundus. Margins of the gallbladder are smooth. Common bile duct is partially seen on this film and is normal.

Case 267, Fig. 1B. Lateral decubitus film during same examination again demonstrates the non-opacified layer (between arrows).

study, previous surgical removal or prior demonstration of gallbladder pathology. The sequence of events in the case presented is, therefore, not widely appreciated although it has been carefully studied and well documented in the literature.

Jutras (1) has shown that the gallbladder contents during intravenous study (Cholegrafin) are not homogeneous. The fresh iodinated bile arriving from the liver is lighter than the non-iodinated concentrated bile and overlays the latter initially. As this iodinated bile is concentrated it sinks to the bottom and the original non-opaque bile is bordered by an opaque floor and an opaque ceiling. These processes occur simultaneously and in non-homogeneous fashion, and numerous bands of changing density have been observed at the same time in



certain gallbladders. Manipulating the patient is of no avail as the layers are discrete and mixing does not occur. Continuing the examination until advanced concentration or partial emptying occurs will usually serve to clarify the picture and avoid an erroneous diagnosis of significant filling defect. This usually occurs within three hours.

Jutras (1) also suggests that since patients who demonstrate the phenomenon of layering can be presumed to have gallbladders that empty poorly and infrequently, they tend to form stones, and he has seen such a development



Case 267, Fig. 2. Erect compression spot film during oral cholecystogram (Telepaque) shows no abnormality.

occur after a four-month interval. Therefore, in these cases he recommends stimulation and complete evacuation of the gallbladder periodically with cholegogues and choleretic drugs.

Although the history of sclerosing cholelithiasis in this case appears to have been established histologically, one may speculate as to whether both episodes of jaundice were in fact caused by the passage of small biliary calculi.

*Case Report:* LAYERING OF BILE DURING INTRAVENOUS CHOLECYSTOGRAPHY.

#### ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Seymour Berkowitz, Good Samaritan Hospital, Suffern, New York.

## REFERENCES

1. Jutras, A.: Cholegraphie Endoveineuse Nouveaux Aspects De Physiologie Biliaire Calculs Flottants, *L'Union Med. Canada*, 83: 3, 1954.

## CASE NO. 268

A 32-year old male was admitted to the hospital with complaints of weakness and shortness of breath on exertion. Routine laboratory data revealed a hemoglobin of 6 gms and a stool guaiac reaction of 4 plus. Past history revealed that the patient underwent an appendectomy and umbilical herniorrhaphy at the age of 12 at which time the surgeon described a loop of dilated and thickened small bowel. There was no apparent obstruction and no biopsy or resection was performed. Two years prior to admission the patient complained of back pain and pyrosis. Gastrointestinal series and cholecystography were performed at another institution and reported as normal.

A gastrointestinal series was performed. The esophagus, stomach and duodenum were intrinsically normal. The jejunal loops showed no abnormality. Barium then filled an enormous bilobed sac which measured 20 by 15 cm in greatest diameter. Multiple lucent filling defects within the sac were interpreted as residual secretions and ingested material. A loop of small bowel located in the right upper quadrant just proximal to this large sac was moderately dilated. Delayed films revealed retention of opaque material in the sac. Some loops of ileum were identified distal to the sac and these were of normal caliber (Fig 1). The cecum was located more medial than usually seen, apparently mobile. Barium enema examination showed the colon to be intrinsically normal with a mobile cecum. Reflux into a few terminal ileal loops showed no intrinsic abnormality. Differential diagnosis included Meckel's diverticulum, a duplication of the bowel, and a chronic partial obstruction of a small bowel loop, possibly associated with inflammatory disease.

The patient was prepared for surgery. At laparotomy, a very large dilated structure was encountered lying in the lower abdomen and pelvis. The structure was twisted 180 degrees in a clockwise direction. After untwisting, it was seen that the small bowel and the right colon had no mesenteric attachment. There were thick bands which joined the right colon to the region of the duodenum. The large dilated segment was in continuity with the small intestine and was felt to represent a large dilated loop of bowel. It was resected. The bands were lysed and the bowel fixed to the posterior abdominal wall.

Pathological examination revealed a large bilobed diverticulum projecting from the antemesenteric border of a segment of ileum, measuring 12 cm in maximum diameter. The diverticulum contained undigested vegetable matter and fecal matter. The mucosa was coarse and appeared on gross examination more like gastric mucosa than small intestinal mucosa; however, random sections showed only small intestinal mucosa. No ulcer was seen. The structure was classified as a giant Meckel's diverticulum.

Although Meckel's diverticula occur in 2 per cent of the population (1), only a small proportion of these are symptomatic. Embryologically, Meckel's diver-



Case 268, Fig. 1. Abdominal radiograph during a small bowel series shows an enormous bilobed sac measuring 20 by 15 cm in greatest diameters. Considerable amount of retained secretions and particulate matter ("gunk") is noted at the bottom of the structure. A loop of small bowel in the right upper quadrant is moderately dilated and proved to be just proximal to the sac in continuity.

ticulum represents a vestige of the vitelline duct and is therefore always situated on the antemesenteric border of the ileum, usually about 30 cm from the ileocecal valve; on rare occasions it can be found as far as 1 meter proximal to the valve. The symptoms related to Meckel's diverticula are either those pertaining to mechanical obstruction, hemorrhage, intussusception or volvulus. Hemorrhage

is usually due to peptic ulceration from heterotopic gastric mucosa. It may attain a large size that may produce mechanical obstruction. Marshak et al reported a large Meckel's diverticulum measuring 9 by 10 cm in diameter with many surrounding adhesions which caused symptoms of chronic intestinal obstruction (2). Another similar large diverticulum was described by Feist et al which measured 10 cm in diameter (3). It also produced evidence of chronic intestinal obstruction. The present case measured 10 cm in diameter and produced both guaiac positive stool and intermittent vague abdominal pain.

*Case Report: GIANT MECKEL'S DIVERTICULUM.*

#### ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Elias Tsoukas, Good Samaritan Hospital, Suffern, N. Y.

#### REFERENCES

1. Bockus, H. L.: Gastroenterology, ed 2, Philadelphia: W. B. Saunders Co., 1965, vol 2, p 91.
2. Marshak, R. H., and Friednan, A. I.: Meckel's diverticulum producing Chronic Intestinal Obstruction, *Gastroenterology* 15: 754, 1950.
3. Feist, J. H., and Wilde, R. C.: Symptomatic Meckel's Diverticulum of unusually large size, *Am. J. Roentgenol.* 83: 882, 1960.

#### CASE NO. 269

A 4½-year old male child was referred for out-patient radiographic studies of the urinary tract. During the previous six weeks the patient had experienced bouts of high fever with no positive physical finding. A urinalysis was reported as negative but a second urinalysis revealed pyuria. Past history was otherwise noncontributory.

An intravenous pyelogram was performed. The study revealed bilateral duplicated collecting systems. One of the ureters on the left side was dilated and tortuous. The bladder was large. A peculiar collection of opaque material was seen through the bladder on the left side of the pelvis (Fig 1).

The patient returned several days later for voiding cystourethrography. Following catheterization and instillation of opaque material into the bladder, a diverticulum filled from the floor of the bladder projecting to the left. Some reflux of opaque material into one of the left-sided ureters also occurred (Fig 2A). The bladder emptied well during the act of voiding; the urethra was well demonstrated and was normal. However, the contrast material which had entered the diverticulum and left ureter then returned to the bladder and distended it. Although the patient no longer experienced the urge to void, considerable residual urine was present (Fig 2B).

#### DISCUSSION

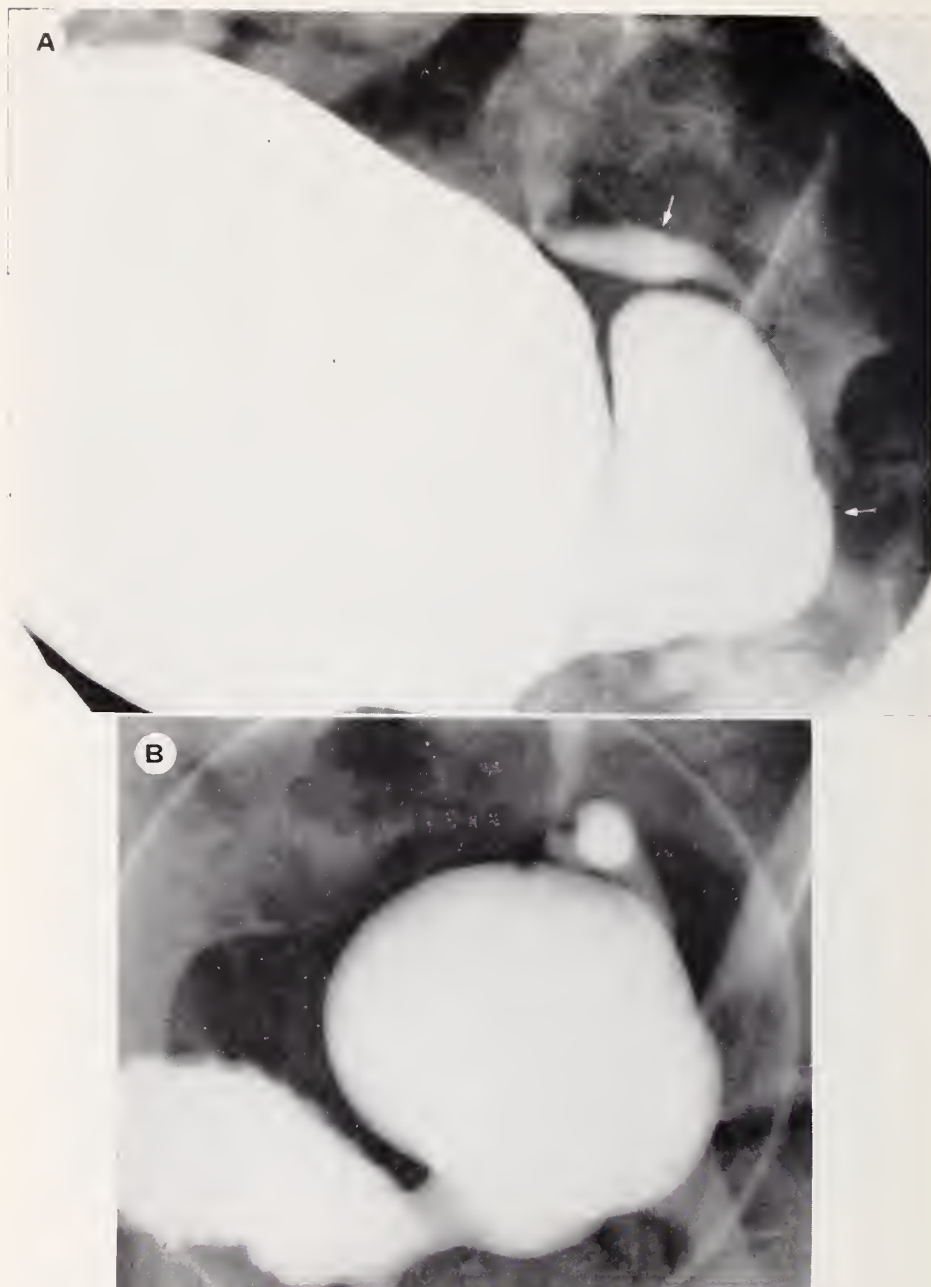
See discussion following Case No. 270.

*Case Report: CONGENITAL DIVERTICULUM OF BLADDER FLOOR.*



Case 269, Fig. 1. Abdominal radiograph from an intravenous pyelogram reveals bilateral duplication of urinary collecting systems. One of the ureters is dilated and tortuous on the left side (along upper arrows). Bladder is large. A comma shaped collection of opaque material is seen through the bladder on left side of the pelvis (lower arrow).





Case 269, Fig. 2A. Oblique radiograph of the pelvis from a cystogram shows an opacified diverticulum originating from floor of bladder (lower arrow). A small amount of reflux is seen in one of the left-sided ureters (upper arrow).

## ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Sidney Berezin, Good Samaritan Hospital, Suffern, N. Y.

## CASE NO. 270

An 11-month-old male infant was in good health until several days prior to admission, at which time the mother noted apparent abdominal tenderness and difficulty in having bowel movements. On admission to the hospital, physical examination revealed moderate abdominal distention. There was some suprapubic tenderness to palpation. On rectal examination a mass was palpated anteriorly.

Routine laboratory examination of the blood and urine revealed no significant abnormality. Blood urea nitrogen was 9 mg/100 cc.

Routine chest X-ray was normal. Plain film study of the abdomen revealed a pelvic mass suggesting a distended bladder. Intravenous pyelogram revealed prompt function bilaterally. Bilateral hydronephrosis and hydroureter was evident. A film made at one hour showed a very large distended urinary bladder with a large posterior extension reaching to the sacrum, interpreted as a large diverticulum of the floor of the bladder. Both lower ureters were displaced to the right with the left ureter arched across the top of the diverticulum (Fig 1A). A 24-hour film confirmed the marked bladder distention and diverticulum formation (Fig 1B).

The bladder was then catheterized and 450 cc of urine was removed. Contrast material was introduced and a voiding cystourethrogram was performed. A lateral view revealed the bladder and diverticulum joined by a narrow neck (Fig 2). The study was not successful in demonstrating the urethra.

The patient was transferred to another institution where cineradiographic studies of the bladder and urethra were performed during the act of voiding. The study demonstrated that during the act of voiding the bladder emptied mainly into the diverticulum and only a small amount of opaque material passed through a normal urethra. As the diverticulum filled it exerted extrinsic pressure on the trigone and produced a functional obstruction. Following completion of the act of voiding, opaque material from the diverticulum refilled the bladder, thus producing a large residual urine.

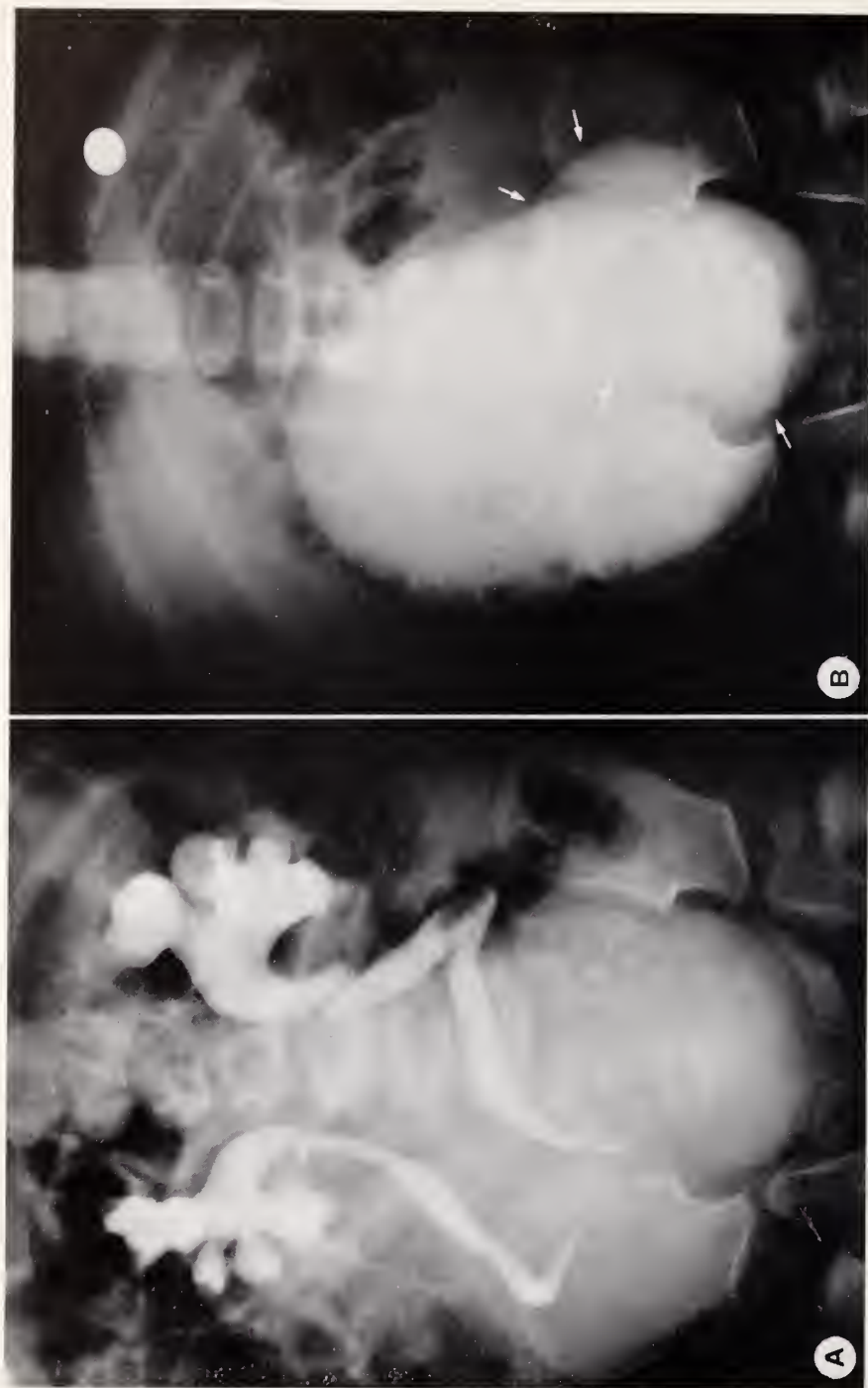
With the information gained from this demonstration of the trigonal anatomy, the patient was referred for urological surgery. The diverticulum was successfully resected.

## DISCUSSION

Diverticulum of the bladder is one of the less common mechanical problems in pediatric urology. Early thinking suggested that these were

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Case 269, Fig. 2B. Radiograph made during the act of voiding shows the empty bladder with normal mucosa. The smoothly contoured diverticulum is opacified. Opaque material from this diverticulum then refilled the bladder but the patient no longer had an urge to void. The urethra was normal (not shown).



Case 270, Fig. 1A. Abdominal radiograph at one hour from an intravenous pyelogram reveals bilateral hydronephrosis and hydroureter. Lower ends of both ureters are displaced upwards and to the right. Bladder is huge and poorly opacified.

Case 270, Fig. 1B. Abdominal radiograph at 24 hours reveals enormous distention of bladder. The diverticulum can be seen through the bladder outline (along arrows).

virtually always secondary to obstruction and increased intravesical pressure (1). Many cases have been reported in the more recent literature which document a normal intravesical excretory tract and thus point clearly to congenital etiology. Both Case No. 269 and Case No. 270 belong to this category.

Signs and symptoms of infection, and less commonly, pain on micturition lead to urologic investigation. The ability of the patient to void a second time



Case 270, Fig. 2. Lateral radiograph of the pelvis from cystogram shows bladder and posteriorly located diverticulum joined by a narrow neck.

shortly after completing micturition may be a clue to the diverticular reservoir; however, this is not a specific sign.

Most of these diverticula are globular, narrow-necked, and take origin in relation to the trigone. Such are the cases presented. Others may be of a more diffuse variety and originate at some distance from the trigone. Reflux appears to be related to the proximity of the diverticular and ureteral orifices such that the normal valve-like mechanism at the uretero-vesical junction is impaired (2).

The treatment is surgical. Histological examination of the diverticular walls reveals in general a sparseness of muscle fibers with an abundance of fibrous tissue, consistent with a congenital etiology.

*Case Report: CONGENITAL DIVERTICULUM OF BLADDER FLOOR.*

## ACKNOWLEDGMENTS

This case is presented through the courtesy of Dr. Sidney W. Berezin, Good Samaritan Hospital, Suffern, N. Y.

The information regarding the cineradiographic study is presented through the courtesy of Dr. Walter E. Berdon, Babies Hospital, New York.

## REFERENCES

1. Campbell, M.: Clinical Pediatric Urology, Philadelphia: W. B. Saunders Company, 1951, pp 257-261.
2. MacKellar, A., and Stephens, F. D.: Vesical Diverticula in Children, Australian & New Zealand J. Surg. 30: 20, 1960.

## CASE NO. 271

This 26 year old female was seen in the obstetrical outpatient department in the first trimester of pregnancy. A routine chest X-ray revealed a well demarcated elliptical density in the right lower lung field (Fig 1, between ar-



Case 271, Fig. 1. There is a well demarcated elliptical radiopaque density in the right lower lung field (between arrows). The long axis of this density is oblique, pointing downwards and outwards. There are numerous tiny lucencies in this area giving it a speckled appearance.



rows). The long axis of the density was oblique, pointing downwards and outwards. Careful scrutiny of this extra density revealed it to be speckled in character, with small punctate lucencies between the denser areas. The remainder of the lung fields appeared normal. A chest roentgenogram taken 2 years previously showed no abnormalities of the right lower lung field (Fig 2).

Because of the previous normal chest X-ray and the peculiar shape and



Case 271, Fig. 2. Normal Chest Roentgenogram.

polarity of the right lower lobe density, a careful history was taken which revealed that 6 months before the last roentgenogram, the patient had aspirated an enteric coated popular "cold capsule". The patient experienced a severe coughing spell at that time but had been completely asymptomatic since.

#### DISCUSSION

Enteric coated capsules can apparently remain asymptomatic and dormant in a peripheral bronchus since there are no proteolytic enzymes within the bronchus to dissolve the capsule. In the case presented, there was no evidence of peripheral atelectasis. It became quite important to recognize that the density in the right lower lobe represented a foreign body and not a granuloma as this pa-

tient was pregnant and the latter diagnosis would have necessitated further investigation and possible treatment. If the possibility of an aspirated capsule is kept in mind, its identity is easily recognizable because of its elliptical smooth shape and its peculiar speckled density.

*Case Report:* ASPIRATED CAPSULE IN RIGHT LOWER LOBE.

#### ACKNOWLEDGMENT

The editors wish to thank Dr. Henry L. Dorfmann for permission to publish this case.

*Submitted for publication August 5, 1966.*

## In Memoriam

FRANKLIN HOLLANDER, PH.D.

1899–1966

Franklin Hollander died at his home March 24 after a long illness borne stoically. He had been chief of the Gastrointestinal Research Laboratory and Attending Gastrointestinal Physiologist at The Mount Sinai Hospital for many years.

Franklin Hollander was born January 19, 1899 and was educated in New York City, receiving his B.S. from Columbia in 1919 and his Ph.D. from the same university in 1924 in the field of Physical Organic Chemistry. After a year spent, interestingly enough, as an industrial chemist, came the turning point in his career as a biologist of the gastrointestinal tract: Hollander studied at Yale from 1925 to 1927 as Medical Fellow of the National Research Council in Lafayette Mendel's Department of Physiological Chemistry. There he began his rewarding studies on gastric secretion. These were continued from 1927 to 1932 as Assistant Professor of Physiology at New York Medical College. He spent his summers at the Biological Laboratory, Cold Spring Harbor, each year transporting his pouch dogs and glassware by car from the city to the laboratory on Long Island. After a foray into another area of research, dental caries, at Columbia University, Franklin Hollander came in 1936 to Mount Sinai Hospital in New York where he remained until his death.

Dr. Hollander's fundamental contributions were to the problems of gastric secretion. Combining the meticulous precision of his analytic chemistry with rigorous statistical methods, Hollander shed light on fundamental mechanisms of acid secretion. To the disordered and chaotic welter of conflicting evidence, he brought order and clarity by demonstrating the consistency of the highly acid secretion of the parietal cell, its relation to the tonicity of the blood and its interplay with the nonparietal component whose composition, he discovered, resembles interstitial fluid. The two-component theory remains, after thirty years of inquiry, a model of lucidity and simplicity in accounting for the variations of gastric acidity.

Hollander then turned with a natural logic to the study of that most difficult of substances, gastric mucus. A long series of fundamental studies were concerned not only with the chemical nature of this important biological material, but as always in his work, with the physiological nature of its functions. From this arose the concept of the protective mucous barrier, which has given meaning to the idea of "mucosal resistance" in the study of ulcer.

An outstanding feature of Franklin Hollander's scientific career had been his stance as a physiologist speaking to clinicians and clinical investigators in



FRANKLIN HOLLANDER, PH.D.  
1899-1966

his own hospital, and in his scientific societies and their journals. At Mount Sinai Hospital, Franklin Hollander was the "Physiologist to the Hospital" long before the term became fashionable. He always saw the relations between his basic research and its possible clinical applications. The most striking illustration of this was his study of vagal innervation of the canine stomach which led to the development of the insulin test of vagal continuity in man, commonly referred to as the Hollander test. Another more recent example was his study on movement of serum proteins into gastric mucus, which he immediately perceived as relevant to the problem of protein losing enteropathy.

He served Gastroenterology as Associate Editor of the *American Journal of Digestive Diseases and Nutrition* from 1939-1943, Associate Editor of *Gastroenterology* from 1943-1953 and Editor in Charge of Abstracts since 1953; he served Physiology as a member of the Editorial Board of the *American Journal of Physiology*, and, since 1961, *The Journal of Applied Physiology* and he had been Section Editor in Gastrointestinal Physiology for these journals since 1963.

Franklin Hollander was a member of many scientific societies including Sigma Xi, The American Physiological Society, The American Society of Biological Chemists and The Society for Experimental Biology and Medicine.

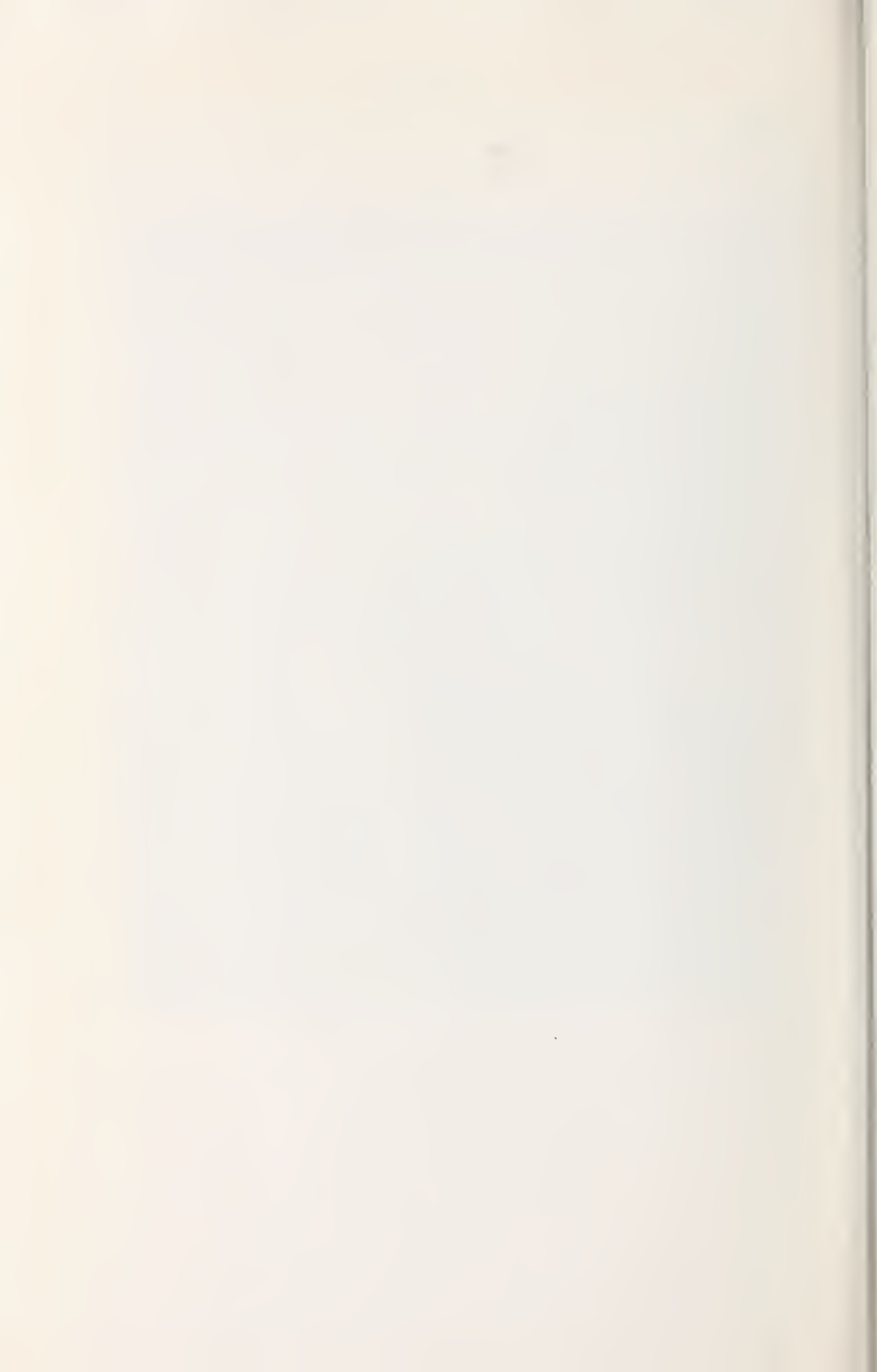
An outstanding trait was his constant receptive attitude to the young. He treated young investigators with interest and grave courtesy, receiving them not only in his laboratory but into his home.

In Gastrointestinal Physiology he was of the generation of Cannon, Carlson, Babkin, Mann and Bollman, and shared with them in 1965 the Julius Friedenwald Medal of the American Gastroenterological Association "for outstanding achievement in gastroenterology."

Franklin Hollander is survived by his widow Muriel and two sons; Michael, an architect, and John, a poet and professor of literature at Yale.

HENRY D. JANOWITZ, M.D.  
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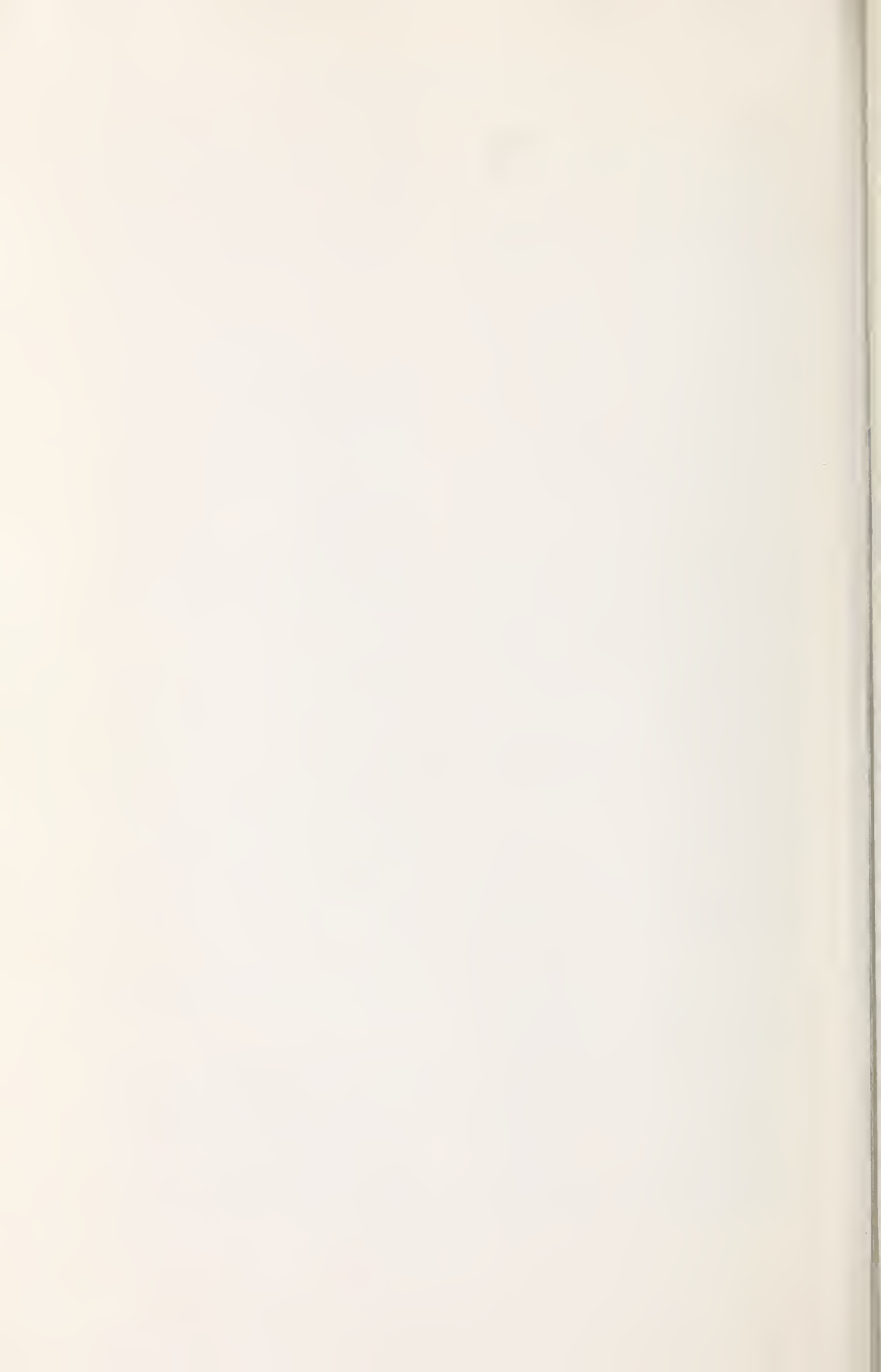
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